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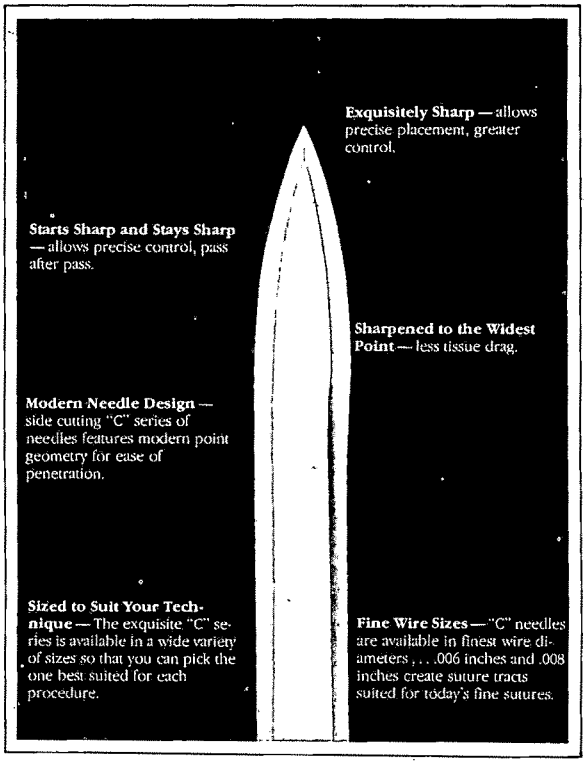
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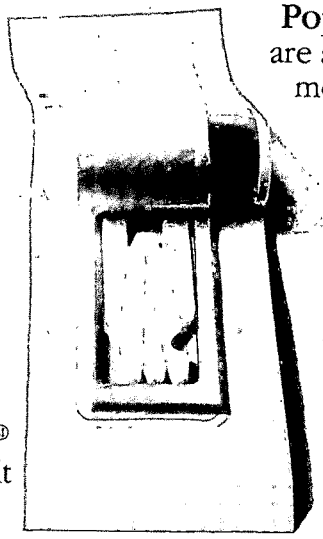


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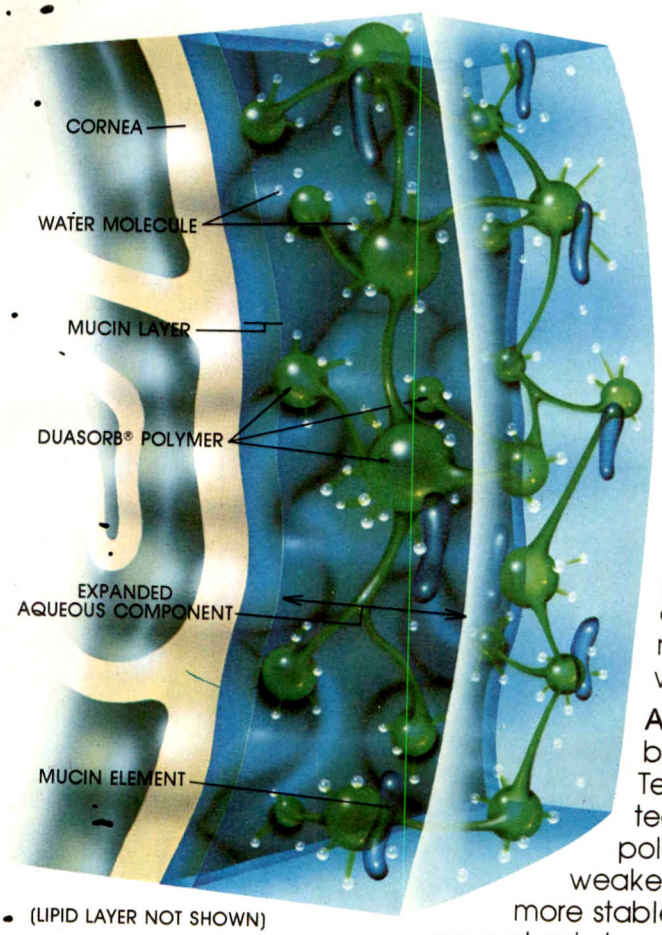
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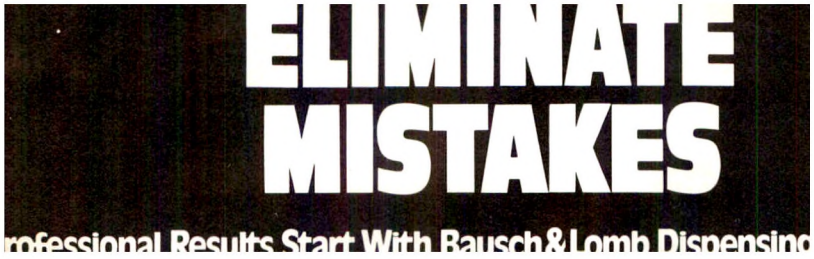
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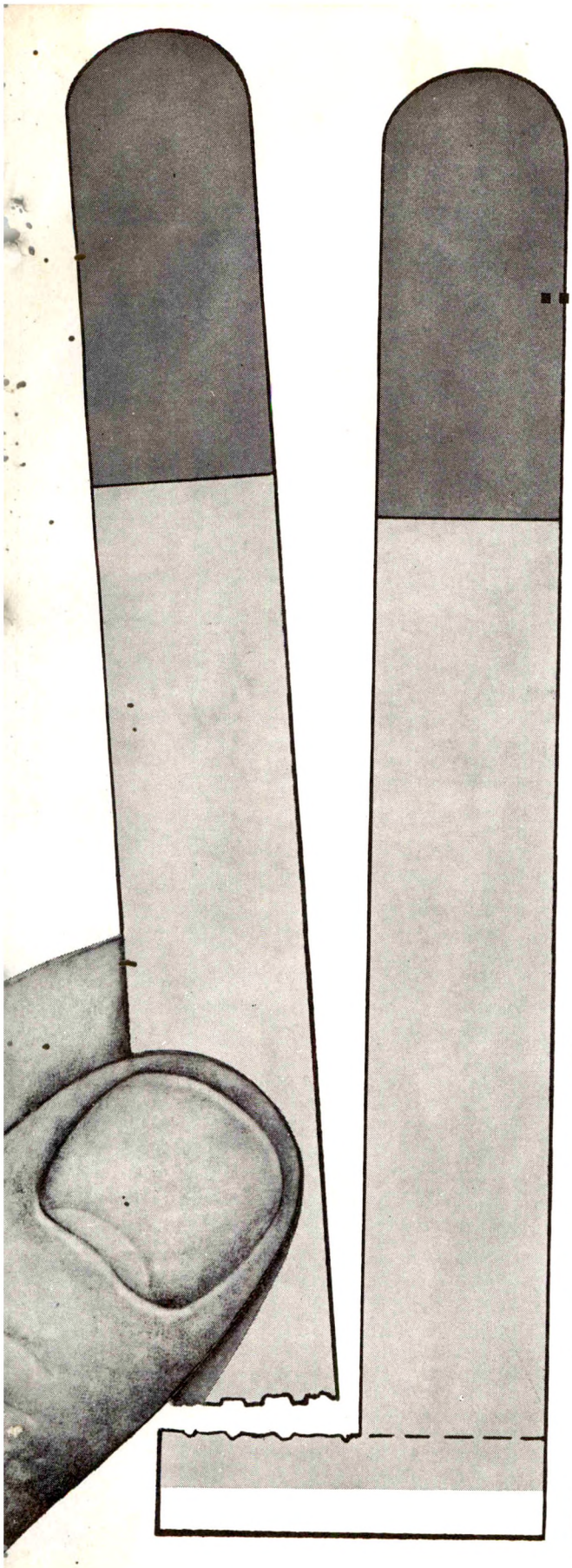
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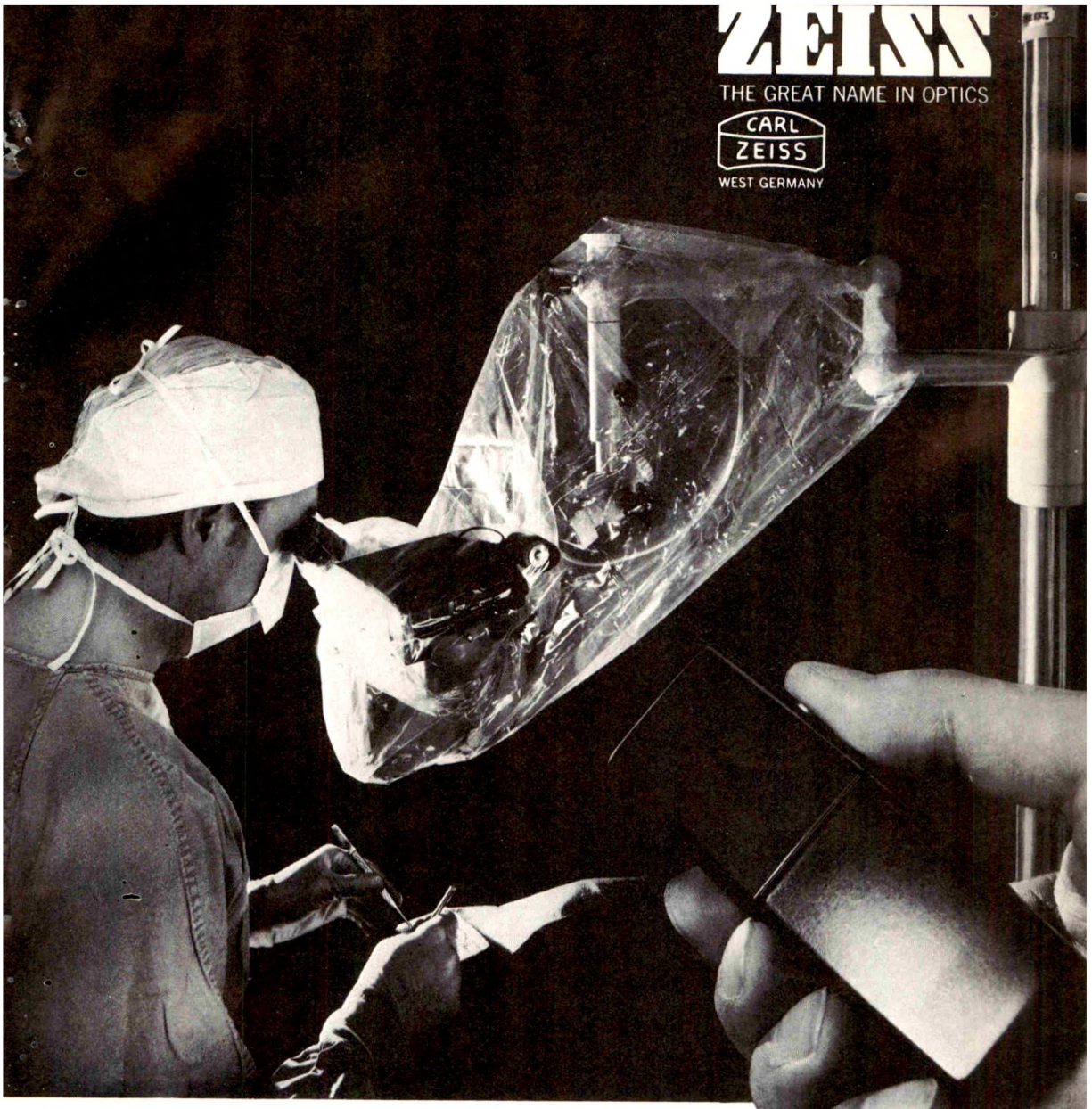
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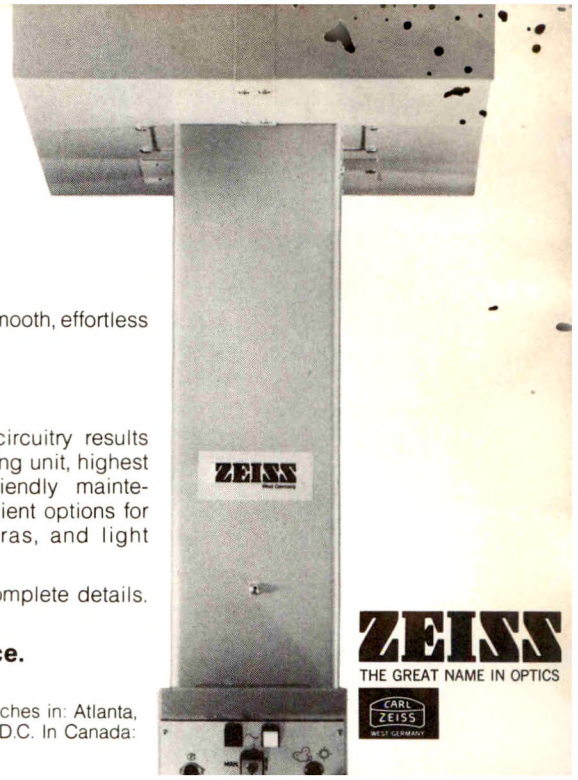
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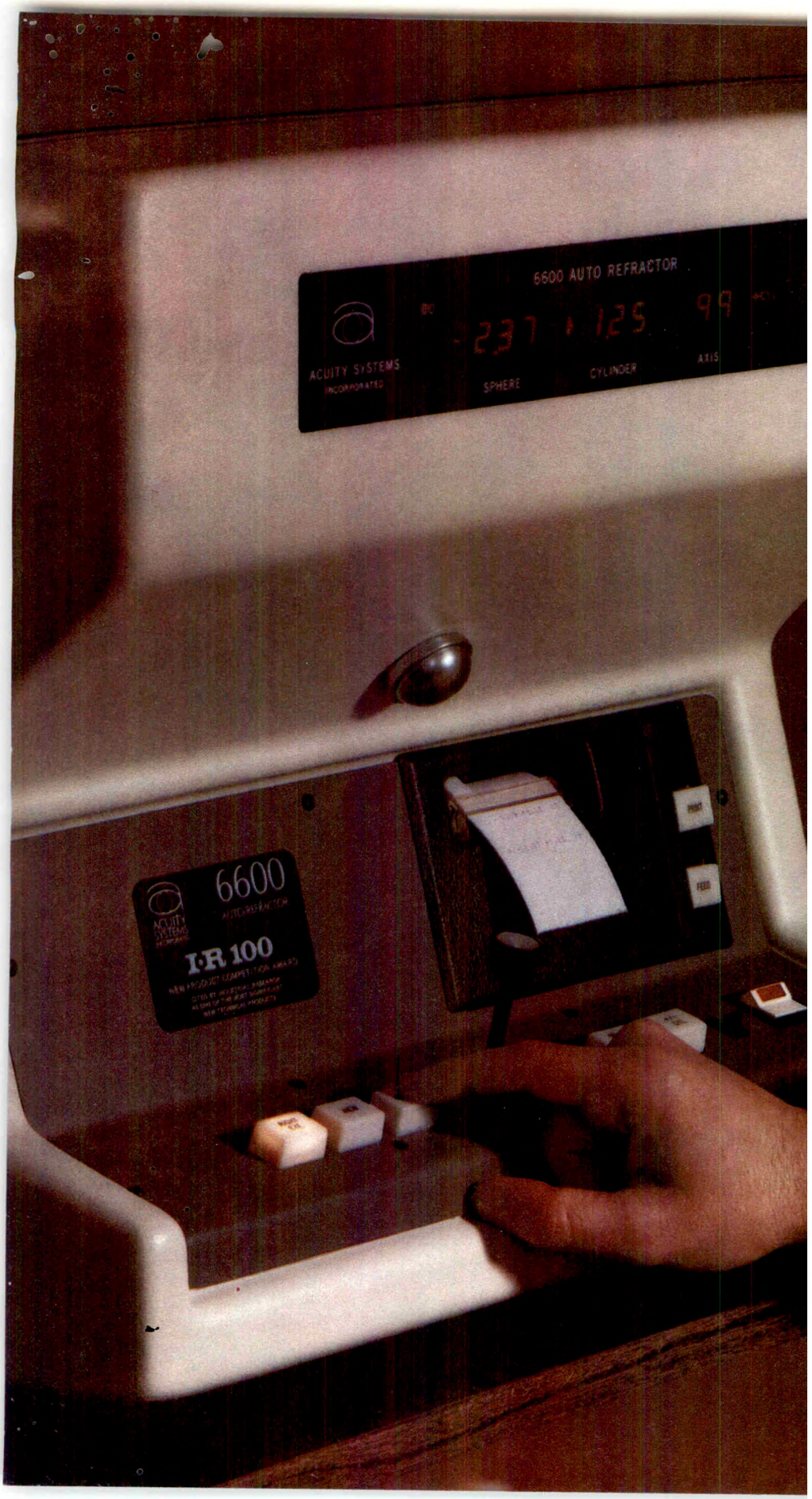
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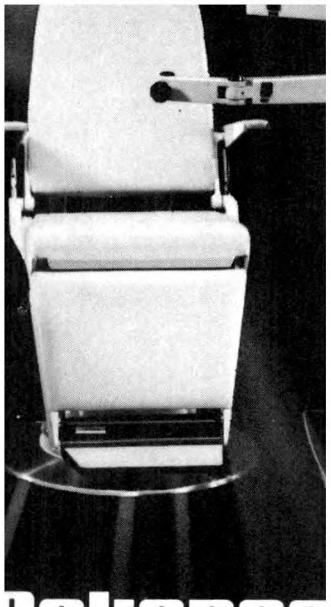
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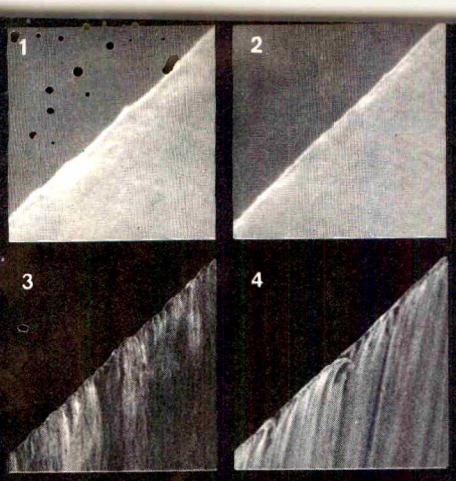
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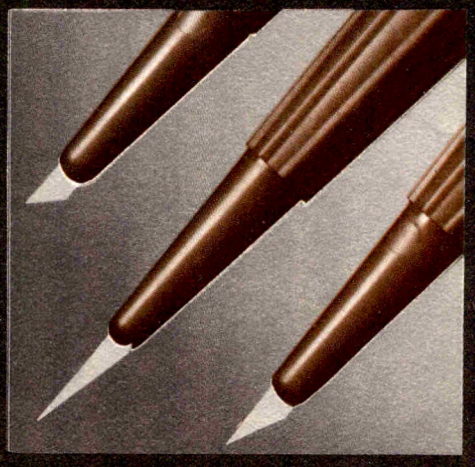
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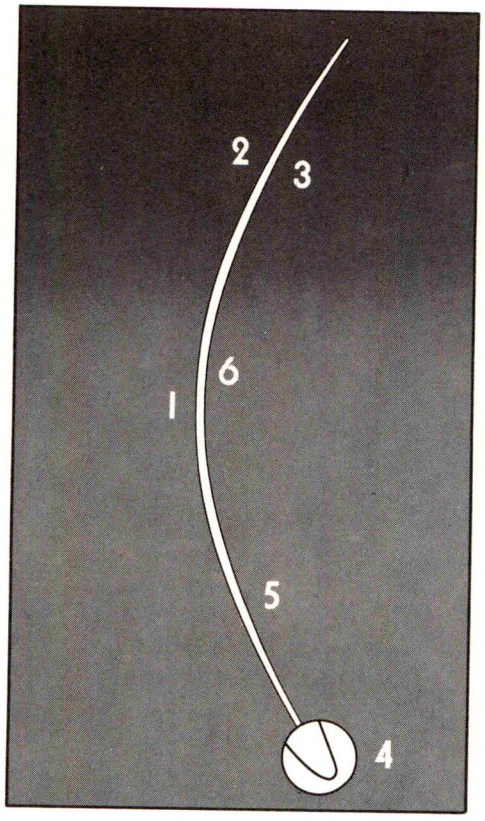
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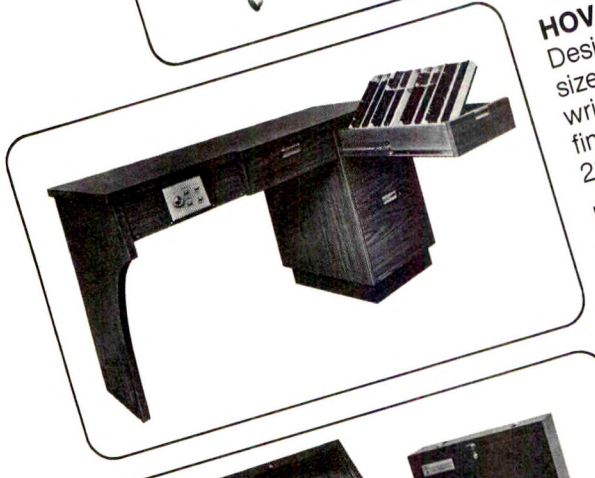
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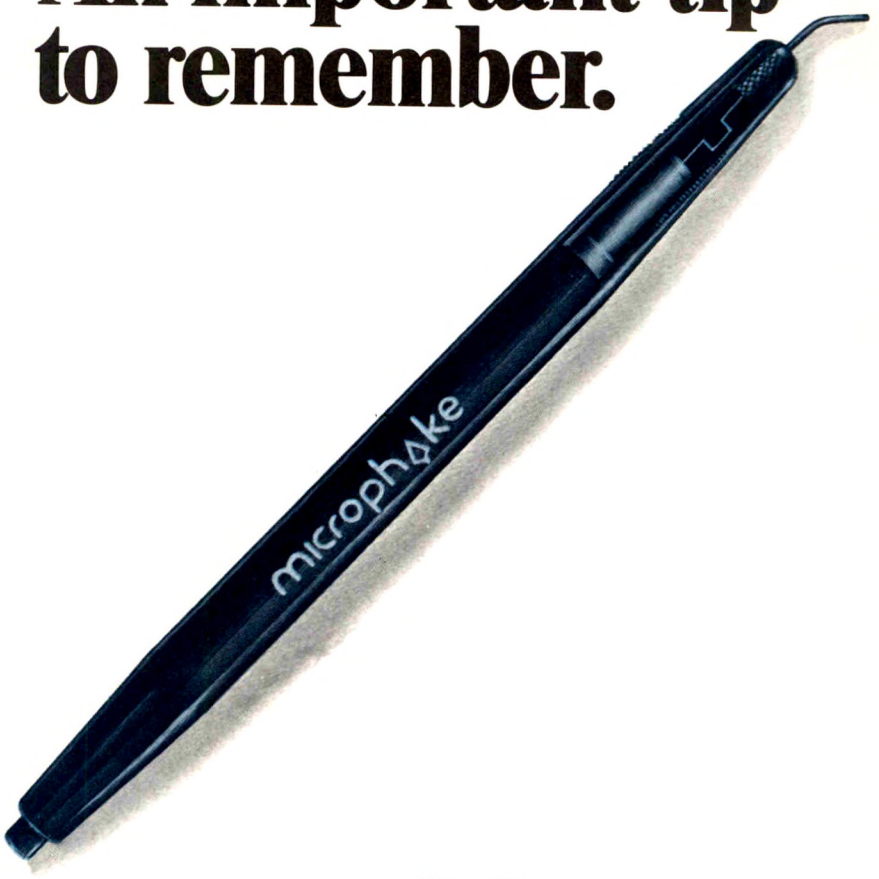
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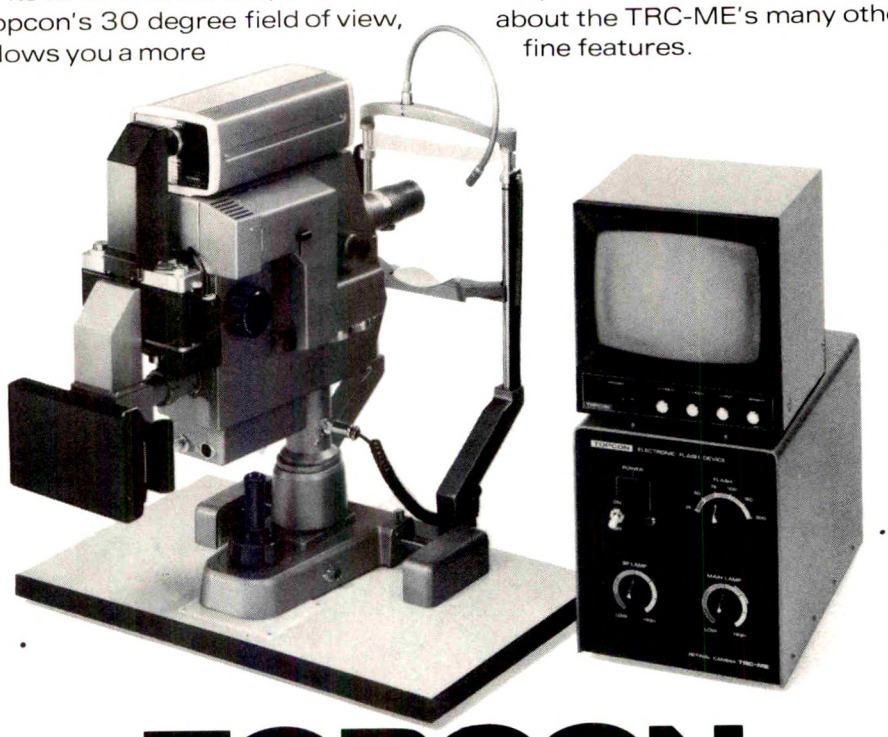
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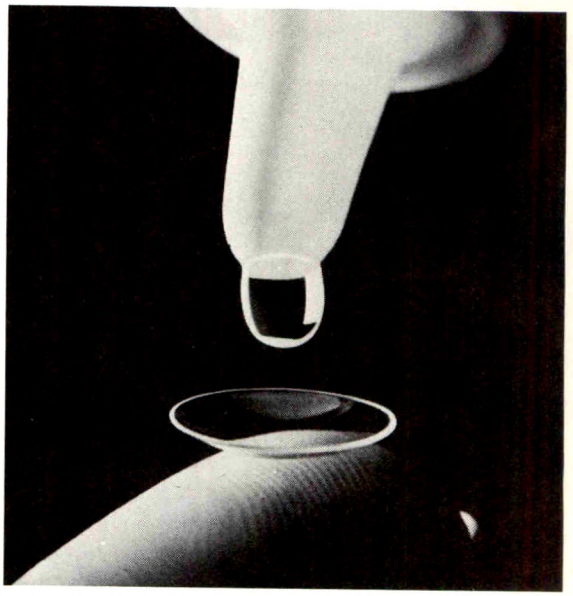
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In diagnosis... One drop of PHOSPHOLINE IODIDE 0.125% instilled daily in each eye prior to retiring, for two or three weeks, will help to determine if there is an accommodative basis for the esotropia.

In treatment... If there is a significant accommodative factor present, the continued use of PHOSPHOLINE IODIDE alone is often sufficient to correct the problem, as long as the drug is well tolerated. PHOSPHOLINE IODIDE acts by altering the accommodative convergence/accommodation relationship in a favorable way, so that near vision is obtained with less accommodative effort and fusion can frequently be reestablished.
If corrective lenses are necessary, PHOSPHOLINE IODIDE may permit the use of single vision lenses instead of bifocals.
If surgery is necessary, postoperative use of PHOSPHOLINE IODIDE may help correct a residual deviation.

P 24,308

BRIEF SUMMARY
(For full prescribing information, see package circular.)
PHOSPHOLINE IODIDE®
(ECHOTHIOPHATE IODIDE FOR OPHTHALMIC SOLUTION)
PHOSPHOLINE IODIDE is a long-acting cholinesterase inhibitor for topical use.
Indications: Glaucoma – Chronic open-angle glaucoma. Subacute or chronic angle-closure glaucoma after iridectomy or where surgery is refused or contraindicated. Certain non-uveitic secondary types of glaucoma, especially glaucoma following cataract surgery.
Accommodative esotropia – Concomitant esotropias with a significant accommodative component.
Contraindications: 1. Active uveal inflammation.
2. Most cases of angle-closure glaucoma, due to the possibility of increasing angle block.
3. Hypersensitivity to the active or inactive ingredients.
Warnings: 1. *Use in Pregnancy.* Safe use of anticholinesterase medications during pregnancy has not been established, nor has the absence of adverse effects on the fetus or on the respiration of the neonate.
2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patients receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.
3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same time undergoing treatment with systemic anticholinesterase medications for myasthenia gravis, because of possible adverse additive effects.
Precautions: 1. Gonioscopy is recommended prior to initiation of therapy.
2. Where there is a quiescent uveitis or a history of this condition, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.
3. While systemic effects are infrequent, proper use of the drug requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into the nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.
4. Temporary discontinuance of medication is necessary if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregularities occur.
5. Patients receiving PHOSPHOLINE IODIDE who are exposed to carbamate or organophosphate type insecticides and pesticides (professional gardeners, farmers, workers in plants manufacturing or formulating such products, etc.) should be warned of the additive systemic effects possible from absorption of the pesticide through the respiratory tract or skin. During periods of exposure to such pesticides, the wearing of respiratory masks, and frequent washing and clothing changes may be advisable.
6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects.
7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.
8. PHOSPHOLINE IODIDE (echothiophate iodide) should be used with great caution, if at all, where there is a prior history of retinal detachment.
Adverse Reactions: 1. Although the relationship, if any, of retinal detachment to the administration of PHOSPHOLINE IODIDE has not been established, retinal detachment has been reported in a few cases during the use of PHOSPHOLINE IODIDE in adult patients without a previous history of this disorder.
2. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.
3. Activation of latent iritis or uveitis may occur.
4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.
5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.
6. Lens opacities occurring in patients under treatment for glaucoma with PHOSPHOLINE IODIDE have been reported and similar changes have been produced experimentally in normal monkeys. Routine examinations should accompany clinical use of the drug.
7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.
Overdosage: Antidotes are atropine, 2 mg parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg per kg intravenously; artificial respiration should be given if necessary.
How Supplied: Four potencies are available: 1.5 mg package for dispensing 0.03% solution; 3.0 mg package for 0.06% solution; 6.25 mg package for 0.125% solution; 12.5 mg package for 0.25% solution. Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chorobutanol (chloral derivative), mannitol, boric acid and exsiccated sodium phosphate.

The Ophthalmos Division
AYERST LABORATORIES
New York, N.Y. 10017

7742

EDUCATIONAL TELEVISION TAPES IN MICROSURGERY BY John L. Fox, M.D. WEST VIRGINIA UNIVERSITY MEDICAL CENTER

In response to multiple requests for these tapes, copies are being made available for purchase. The tapes are one half to one hour long and are available on ¾ inch video cassette or Betamax cassette. All tapes are in color taken through an operating microscope. Specify selection and tape format and send check or institutional purchase order made out to:

Crislip Communications
P.O. Box 205
Maidsville, W.V. 26541

Microvascular Anastomosis:
Carotid Artery of the Rat-1 tape: $190.00
STA—MCA Anastomosis-2 tapes: $170.00 each

FACULTY PLACEMENT SERVICE ASSOCIATION OF UNIVERSITY PROFESSORS OF OPHTHALMOLOGY, INC.

The Faculty Placement Service of the Association of University Professors of Ophthalmology, Inc. is established to aid ophthalmologists, physicians in related fields and vision research scientists interested in becoming associated with University Ophthalmology Programs. This service functions by receiving information from applicants and distributing this material to Ophthalmology Program Chairmen.

Application forms may be obtained from the Secretary-Treasurer of the Association of University Professors of Ophthalmology, Inc.

To participate in the Faculty Placement Service, send the completed application form and a registration fee of $15.00 to:

George W. Weinstein, M.D.
Professor and Head
Division of Ophthalmology
University of Texas Medical School at San Antonio
San Antonio, Texas 78284

NEOSPORIN®
Ophthalmic Solution Sterile
(Polymyxin B–Neomycin–Gramicidin)

Each cc contains: Aerosporin® brand Polymyxin B Sulfate 5,000 Units; neomycin sulfate 2.5 mg (equivalent to 1.75 mg neomycin base); gramicidin 0.025 mg. Vehicle contains alcohol 0.5%, thimerosal (preservative) 0.001% and the inactive ingredients propylene glycol, polyoxyethylene polyoxypropylene compound, sodium chloride and purified water.

NEOSPORIN®
Ophthalmic Ointment Sterile
(Polymyxin B–Bacitracin–Neomycin)

Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 Units; zinc bacitracin 400 Units; neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs.

Brief Disclosure below applies to the solution and ointment.

INDICATIONS: For the short-term treatment of superficial external ocular infections caused by organisms susceptible to one or more of the antibiotics.

CONTRAINDICATIONS: Contraindicated in those persons who have shown sensitivity to any of the components.

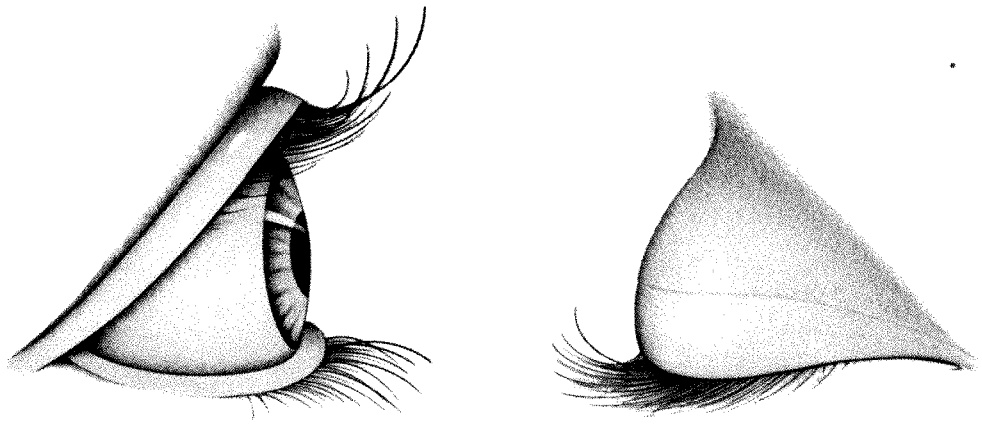
WARNINGS: Prolonged use may result in overgrowth of nonsusceptible organisms. Ophthalmic Ointment may retard corneal healing.

PRECAUTIONS: Culture and susceptibility testing should be performed during treatment.

Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Complete literature available on request from Professional Services Dept. PML.

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709



DAYTIME and NIGHTTIME

Round-the-clock therapy for Superficial External Ocular Infections

For daytime use, the clear solution does not blur vision. For nighttime use, the ointment provides prolonged contact with the infection. In both of these products, triple-overlapping antibiotic formulas are effective against a wide range of gram-negative and gram-positive bacteria. Efficacy has been proven in millions of uses over the past 20 years.

NEOSPORIN®
Ophthalmic Solution
Sterile
(Polymyxin B–Neomycin–Gramicidin)



NEOSPORIN®
Ophthalmic Ointment
Sterile
(Polymyxin B–Bacitracin–Neomycin)

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

See adjacent page for brief prescribing information

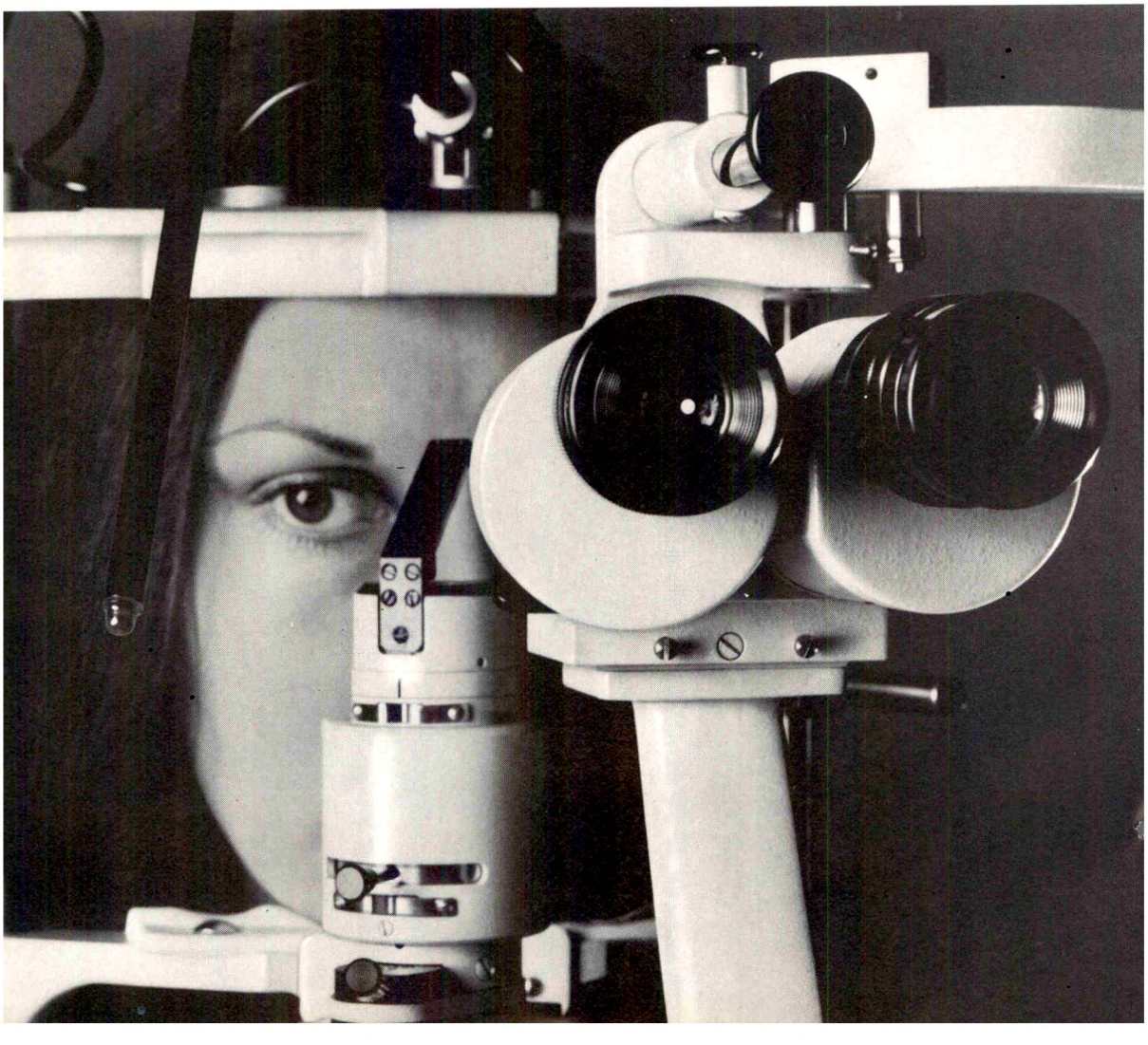
Nikon CS-1 clinical slit-lamp: built to put patients within reach, priced to put purchase within reach.

Only 11 inches separate you and your patient when you use the new Nikon CS-1 slit-lamp microscope. Compact and moderately priced, it is an ideal clinical instrument. Look to Nikon for practicality — and you get it.

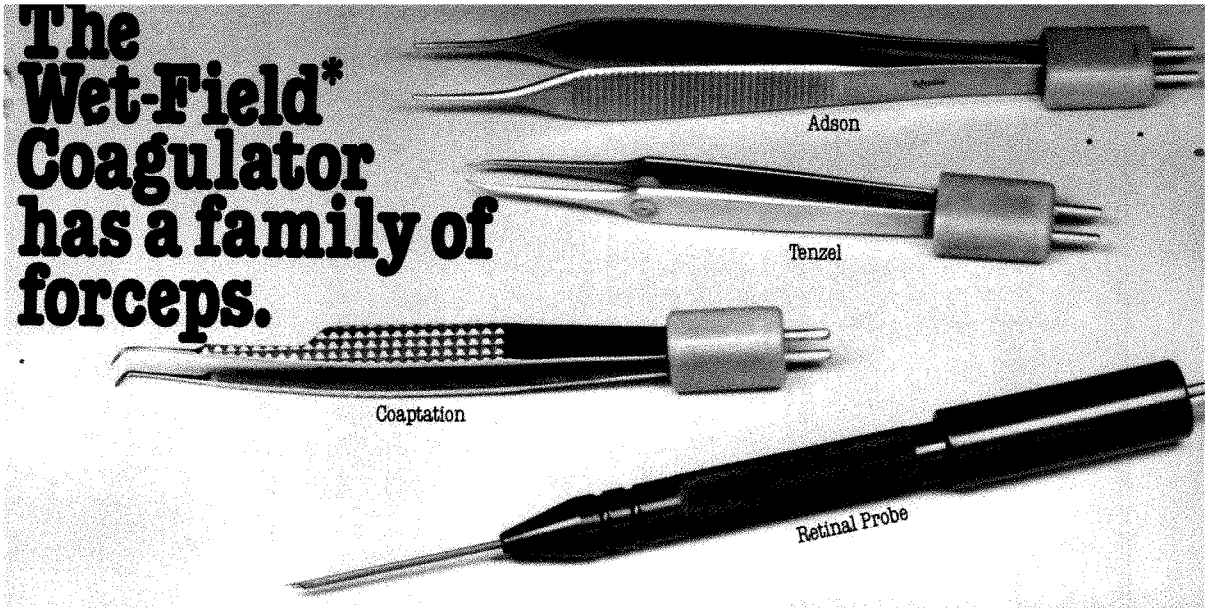
Packed into its small size is an incredible capability. First, Nikon optics, unsurpassed in quality and the crisp, clear image they transmit. The optics are backed by a quartz-halogen illumination system for bright, white light. Human engineering places the slit control directly on the joystick, so that you can adjust the slit width from 0 to 9mm, and rotate it up to 90°. And all other essential controls are grouped for equally simple operation.

The CS-1 is complete, but you can add a precision applanation tonometer that mounts conveniently on the front of the microscope.

Contact Nikon Inc., Instrument Division, subsidiary of Ehrenreich Photo-Optical Industries, Inc., 623 Stewart Ave., Garden City, N.Y. 11530; (516) 222-0200. **Look to *Nikon***



The Wet-Field* Coagulator has a family of forceps.



Our Wet-Field Coagulator keeps a versatile family of precision forceps – a growing family:

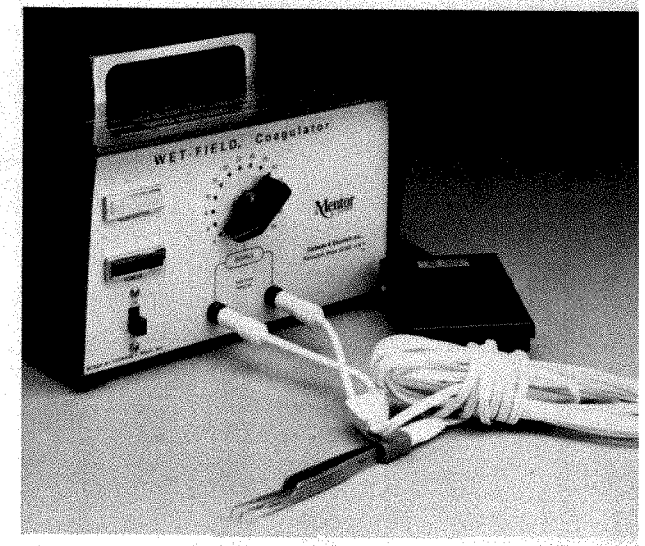
Straight and curved iris forceps; Adson forceps for ophthalmic plastic surgery; coaptation forceps for sutureless closing of the conjunctiva; and the intraocular probe for retinal bleeders. All offer benefits in precision, speed, and minimum trauma to adjacent tissue.

The coaptation forceps, for example, have dramatically speeded the closure of the fornix or limbus base flap after a cataract procedure: One group reports completing the procedure routinely in 20 to 80 seconds by "spot welding" the tissue. Less patient discomfort was noted during healing, and final healing was considered equivalent to suturing.

Wet-Field coaptation forceps have highly polished tips to resist accumulation of coagulated material. In fact, the wet field enhances their basically low-temperature, low voltage operation.

We'd be pleased to demonstrate the Wet-Field Coagulator system and answer any questions about their recent use in eye work. Simply send us the coupon. Or call toll free: 800-225-0462. Mentor Division of Codman, Randolph, Mass. 02368.

©1977 Codman & Shurtleff, Inc.
*Trademark



Free Demonstration

☐ Call me to arrange a demonstration of the Wet-Field Coagulator and its forceps.

Name

Address

Zip

Telephone

Mentor
DIVISION

Please Mark Your Calendar!

OCTOBER						
S	M	T	W	T	F	S
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ANNUAL SCIENTIFIC MEETING

CONTACT LENS ASSOCIATION OF OPHTHALMOLOGISTS, INC.

Monday, October 23, 1978 7:30-10:30 p.m.
Auditorium, Kansas City Convention Center

SYMPOSIUM ON THE MANAGEMENT OF COMPLICATIONS ASSOCIATED WITH THE VARIOUS INTRAOCULAR LENSES

Jack Hartstein, M.D., Moderator

SYMPOSIUM ON THE MANAGEMENT OF COMPLICATIONS ASSOCIATED WITH THE VARIOUS TYPES OF CONTACT LENSES

Jack Hartstein, M.D., Moderator

PARTICIPANTS TO BE ANNOUNCED

No Registration Fee • The Profession is Cordially Invited

JACK HARTSTEIN, M.D.
President

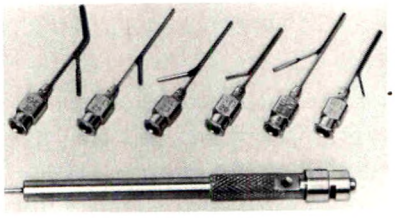
OLIVER H. DABEZIES, JR., M.D., F.A.C.S.
Executive Vice President

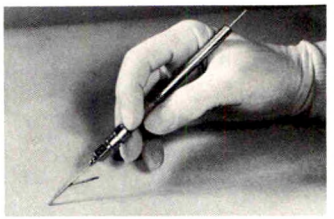
G. PETER HALBERG, M.D., F.A.C.S.
Public Relations Chairman

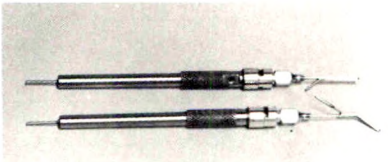
THOMAS* CATARACT ASPIRATION—IRRIGATION SYSTEM

Irrigates and aspirates cortex
Aspirates congenital cataracts easily
Advantageous with phaco emulsifier
Useful in intraocular lens procedures

Significant advantages:
Non-traumatic to corneal endothelium
Self-contained—no machine failures
Irrigation—sterile solution and tubing supplied by the hospital operating room
Aspiration—suction provided per hospital disposable syringe
Finger control port in the handle gives the surgeon absolute control of the entire system
Handle and needles are expertly crafted of stainless steel
Multiple tips available for various techniques
Proven design—in use for over ten years





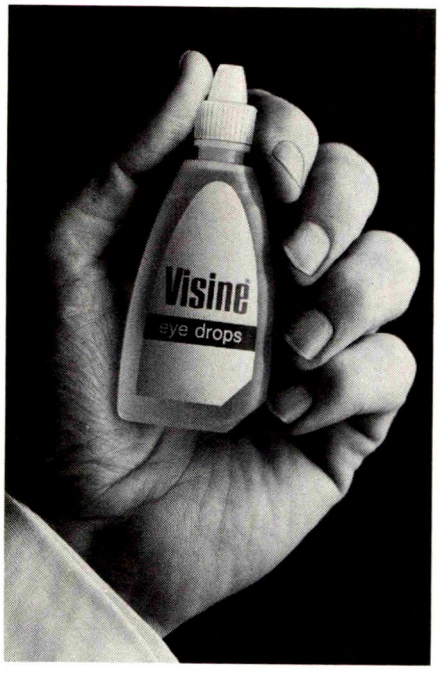


KARL ILG INSTRUMENTS
117 North Charles Avenue
Villa Park, Illinois 60181
(312) 834-4219

*Designed by Edward R. Thomas, M.D.
Dayton, Ohio

IT'S NICE TO KNOW.

Extensive clinical tests* indicate Visine is ideally suited for your recommendation.



Visine® has been proven safe and effective for relief of symptoms of minor eye irritation.

Whatever causes your patients' minor eye irritation—glare, pollen, close work or air pollution—Visine provides fast relief. It relieves the burning and itching, and its vasoconstrictor (tetrahydrozoline HCL) effectively removes redness from the eye.

For this relief, more people already use Visine than any other eye drop. And this widespread acceptance plus Visine's extensive clinical testing means you can recommend Visine to your patients with confidence.

*NDA Clinical #10-878 (1955-'57). Additional NDA Clinical #10-878 (1961). Subsequent Double-Blind Efficacy Studies (8/'72, 9/'76, & 2/'77). ©1978 Pfizer Inc.

Visine Eye Drops is another quality product from Pfizer Inc.

OPHTHALMOLOGIST

Family Health Program, a Federally-certified HMO located in the Southern California area, is looking for an Ophthalmologist to work in one of its modern medical facilities. As a career physician with FHP, you will enjoy the opportunity to practice with one of the country's most progressive medical organizations.

FHP provides the physician with:

- Complete malpractice coverage
- Vacation
- Paid sick leave
- Post-graduate time off
- Paid post-graduate tuition
- Educational leave
- Medical and dental coverage
- Comprehensive retirement plan
- Disability insurance
- Life insurance
- Automobile and MUCH MORE

We have six locations in Southern California, in areas with excellent year-round climate, and located near beaches and mountains.

For more information about this exciting opportunity, write or call collect:

George Weeman, Professional Staffing
(213) 421-4512

FHP

FHP

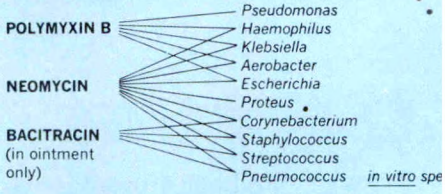
FAMILY HEALTH PROGRAM, INC.
2925 N. Palo Verde Avenue
Long Beach, Calif. 90815



Reserved for you

Nobody knows eyes like an ophthalmologist. That's why we believe products like Cortisporin Ophthalmic Ointment and Suspension should be prescribed only by physicians with special training and knowledge in ophthalmology . . . and why we promote these products only to specialists such as you.

Cortisporin® Ophthalmic Preparations



Wide antibacterial spectrum; gentle anti-inflammatory action

- antibacterial activity against most pathogens likely to be involved in ophthalmic infections accessible to local therapy
- gentle anti-inflammatory action to alleviate swelling, pain, itching, and inhibit corneal neovascularization
- two convenient sterile forms

Please see next page for brief summary of prescribing informatio

Please Mark Your Calendar!

JANUARY

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21	22	23	24	25	26	27
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MID-WINTER NATIONAL MEETING

CONTACT LENS ASSOCIATION OF OPHTHALMOLOGISTS

January 12-14, 1979 • Sahara Hotel, Las Vegas, Nevada

CONRAD BERENS MEMORIAL LECTURE
JORGE N. BUXTON, M.D.
Post Surgical Rehabilitation (Anterior Segment)

DISTINGUISHED VISITING LECTURER
PROFESSOR DR. JOSE BARRAQUER
Present Status of Keratophakia for the Correction of Hyperopia and Aphakia

SYMPOSIA ON CONTACT AND INTRAOCULAR LENSES
CONTACT LENS COURSES **FREE PAPERS**

PRACTICE MANAGEMENT SEMINAR
(Thursday, January 11, 1979)

Free Papers Accepted. Please send abstract to:
Oliver H. Dabezies, Jr., M.D.
Executive Vice President, CLAO
2620 Jena Street
New Orleans, LA 70115

For registration information, contact:
Paul R. Honan, M.D.
1720 Lebanon Street
Lebanon, IN 46052

A special room rate of $34.00 per day (single or double occupancy) has been arranged with the Sahara Hotel. For room reservations only, write the Sahara Hotel, Las Vegas, NV 89114.

Cortisporin® Ophthalmic Ointment Sterile
(Polymyxin B–Bacitracin–Neomycin–Hydrocortisone)

Each gram contains Aerosporin® brand Polymyxin B Sulfate 5,000 units; zinc bacitracin 400 units; neomycin sulfate (equivalent to 3.5 mg neomycin base) 5 mg; hydrocortisone 10 mg (1%); special white petrolatum qs. Tube of ⅛ oz with ophthalmic tip.

Cortisporin® Ophthalmic Suspension Sterile
(Polymyxin B–Neomycin–Hydrocortisone)

Each ml contains Aerosporin® brand Polymyxin B Sulfate 10,000 units; neomycin sulfate (equivalent to 3.5 mg neomycin base) 5 mg; hydrocortisone 10 mg (1%); thimerosal (preservative) 0.001%. The vehicle contains the inactive ingredients cetyl alcohol, glyceryl monostearate, liquid petrolatum, polyoxyl 40 stearate, propylene glycol and purified water. Bottle of 5 ml with sterile dropper.

INDICATIONS: Based on a review of these drugs by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: For the treatment of nonpurulent bacterial infections of the eye due to organisms sensitive to the antibiotic ingredients of the drugs and when the anti-inflammatory action of the hydrocortisone is indicated as in nonpurulent bacterial, allergic, vernal and phlyctenular conjunctivitis; nonpurulent blepharitis; interstitial, sclerosing, postoperative or acne rosacea keratitis; superficial chemical and thermal burns of the cornea.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: These products are contraindicated in acute purulent conjunctivitis and blepharitis; tuberculous, fungal or viral lesions of the skin or eye, including herpes simplex, dendritic keratitis, vaccinia or varicella; and conditions involving the posterior segment of the eye. They are also contraindicated in those individuals who have shown hypersensitivity to any of their components.

PRECAUTIONS: Extended ophthalmic use of topical steroid therapy may result in glaucoma with possible damage of the optic nerves, posterior subcapsular cataract formation, or may aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissues. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids. As with any antibiotic preparation, prolonged use may result in the overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Articles in the current medical literature indicate an increase in the prevalence of persons allergic to neomycin. The possibility of such a reaction should be borne in mind.

Complete literature available on request from Professional Services Dept. PML.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

SEPTEMBER 15 and 16, 1978

OPHTHALMIC ULTRASOUND SEMINARS

Eastern Virginia Medical School
Department of Ophthalmology
Norfolk, Virginia

Host: William Humphrey, M.D.
Hilton Inn
Williamsburg, VA
Course Director: Steve Charles, M.D.

Tuition: Practitioners $250
Residents $175
Technicians $200
(Includes 2 days Hotel and meals)

Contact: Ophthalmic Ultrasound Seminars
c/o Pat Lindgren
P.O. Box 247
Frederick, MD 21701
(301) 694-9494

THE
EDWARD S. HARKNESS EYE INSTITUTE
Columbia-Presbyterian Medical Center
New York, New York

announces

A BASIC SCIENCE COURSE
FOR
Residents in Ophthalmology

September 5, 1978—
December 22, 1978
8:00 A.M. to 12:30 P.M. Daily

Fee: $250.00

Inquire: Miss M. Bowen
635 W. 165th St.
New York, N.Y. 10032
Tel: (212) 694-2725

Sodium SULAMYD®
brand of sodium sulfacetamide, U.S.P.
Ophthalmic Solution 30%, Solution 10%, Ointment 10% – Sterile
INDICATIONS Sodium SULAMYD is indicated for the treatment of conjunctivitis, corneal ulcer, and other superficial ocular infections due to susceptible microorganisms, and as adjunctive treatment in systemic sulfonamide therapy of trachoma.
CONTRAINDICATIONS Hypersensitivity to sulfonamide preparations contraindicates the use of Sodium SULAMYD.
PRECAUTIONS The solutions are incompatible with silver preparations. Ophthalmic ointments may retard corneal healing. Non-susceptible organisms, including fungi, may proliferate with the use of these preparations. Sulfonamides are inactivated by the para-aminobenzoic acid present in purulent exudates. Sulfonamide sensitivity reactions may occur.
June 1972 9838358

METIMYD®
brand of prednisolone acetate, U.S.P., and sulfacetamide sodium, U.S.P.
Ophthalmic Suspension and Ointment – Sterile. Each ml. or Gm. contains 5 mg. prednisolone acetate and 100 mg. sulfacetamide sodium.

INDICATIONS – *Suspension* Based on a review of this drug by the National Academy of Sciences – National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: for the treatment of the following inflammatory and allergic conditions affecting the eyelids and anterior segment of the eye. EYELIDS: allergic blepharitis, blepharitis associated with seborrheic dermatitis and other nonpurulent forms of conjunctivitis including those associated with hay fever, and conjunctivitis due to physical agents such as foreign bodies, chemicals (acids, alkalies) and other irritants. CORNEA, SCLERA, IRIS, AND UVEA: interstitial, postoperative, and sclerosing keratitis; chemical and thermal burns of the cornea; corneal ulcer; herpes zoster ophthalmicus; phylctenular keratoconjunctivitis; corneal neovascularization; scleritis; episcleritis; acute, chronic, and traumatic iridocyclitis.
Final classification of the less-than-effective indications requires further investigation.

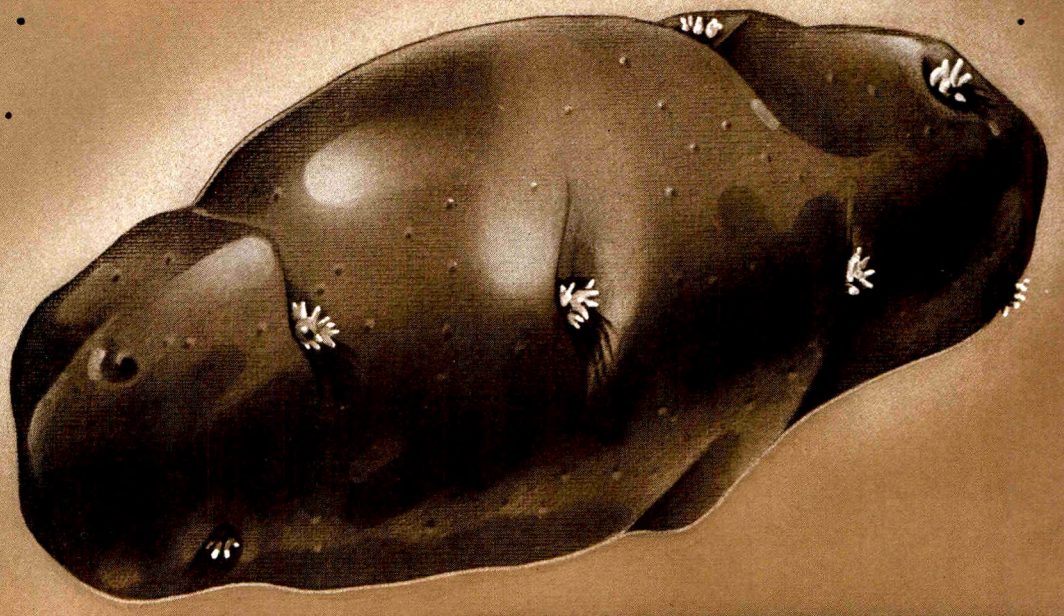
Ointment METIMYD is indicated in the following inflammatory and allergic conditions affecting the eyelids and anterior segment of the eye:
Eyelids: allergic blepharitis; blepharitis associated with seborrheic dermatitis; other nonpurulent types of blepharitis.
Conjunctiva: allergic conjunctivitis, ie, vernal, phylctenular, and other nonpurulent forms of conjunctivitis including those associated with hay fever; conjunctivitis due to physical agents such as foreign bodies, chemicals (acids, alkalies) and other irritants.
Cornea, Sclera, Iris, Uvea: interstitial, postoperative, and sclerosing keratitis; chemical and thermal burns of the cornea; corneal ulcer; herpes zoster ophthalmicus; phlyctenular keratoconjunctivitis; corneal neovascularization; scleritis, episcleritis; acute, chronic, and traumatic iridocyclitis.
In deep-seated infections, such as endophthalmitis, panophthalmitis, and orbital cellulitis, or when systemic infection threatens, specific oral (antibiotic, sulfonamide) therapy should be employed. Local treatment may be used as adjunctive therapy.
CONTRAINDICATIONS The contraindications for METIMYD are the same as those for other corticosteroid-sulfonamide preparations. Topical ophthalmic corticosteroid preparations and combinations are contraindicated in: early acute herpes simplex and the early acute stages of most other viral diseases of the cornea and conjuctiva; active tuberculosis of the anterior segment of the eye; fungal disease of the cornea, conjunctiva and lids; acute purulent untreated infections of the eye which, like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid; individuals with known sensitivity to any of the ingredients.
PRECAUTIONS Extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. In prolonged therapy, it is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to have occurred with the use of topical steroids. As with any antibacterial preparation, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate measures should be instituted. Sensitivity reactions may occur in certain individuals. If signs of sensitivity develop, discontinue use.
The protracted use of topical corticosteroids in the eye reportedly has been rarely associated with the development of posterior subcapsular cataracts.
January 1973, July 1973 9835356, 10106524

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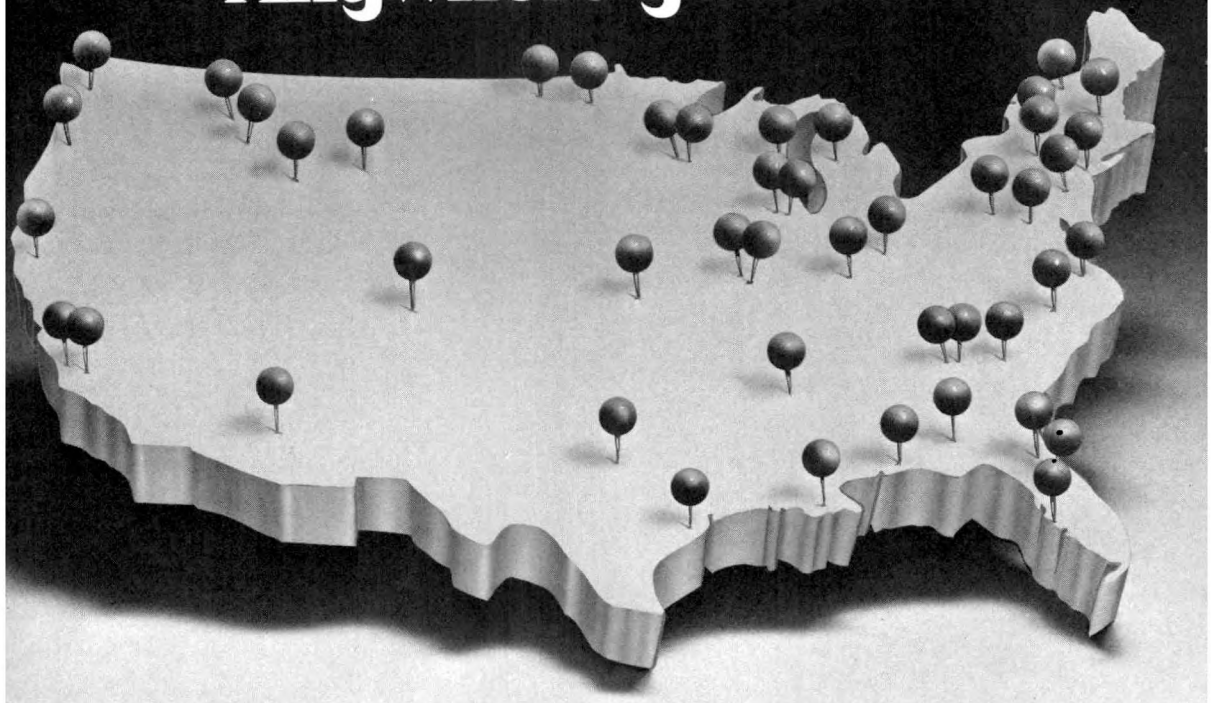
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Before prescribing, please see full product information, brief summaries of which appear on opposite page.

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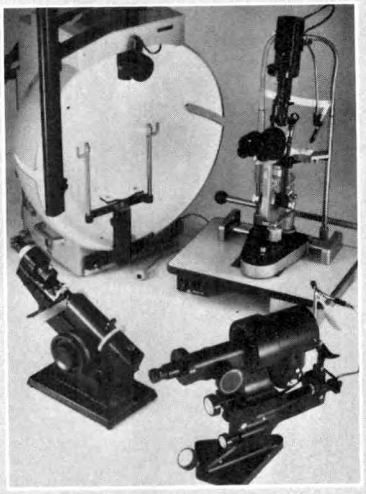


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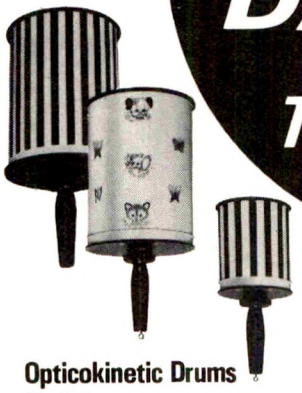
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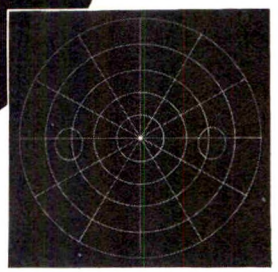
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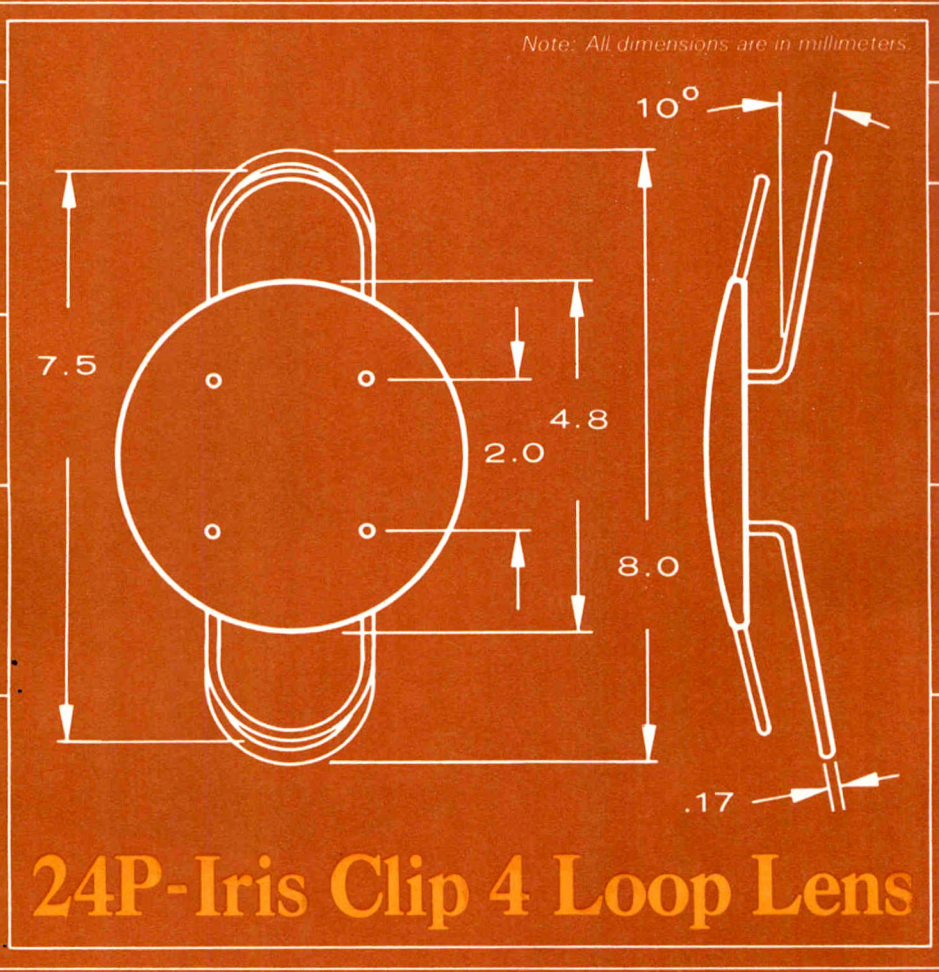
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1. Data on file. American Optical Corp., Soft Contact Lens Div., Southbridge, MA 01550.

See next page for prescribing information.

AOSOFT®
(tetrafilcon A)
HYDROPHILIC CONTACT LENSES

American Optical Corp.
SOFT CONTACT LENS DIV.
Southbridge, MA 01550

AOSOFT® (tetrafilcon A) Hydrophilic Contact Lenses

DESCRIPTION

AOSOFT® (tetrafilcon A) Hydrophilic Contact Lens is a hemispherical shell which covers the cornea and may cover a portion of the adjacent sclera. The lens material, tetrafilcon A, is a hydrophilic random terpolymer of 2-hydroxyethyl methacrylate, N-vinyl-2-pyrrolidone and methylmethacrylate. The polymer is a three-dimensional network of terpolymer chains joined by divinylbenzene cross-links. It consists of 57.5% tetrafilcon A and 42.5% water by weight when fully hydrated in 0.9% sodium chloride solution buffered with monobasic and dibasic sodium phosphates.

ACTIONS

In its hydrated state, the AOSOFT® Hydrophilic Contact Lens is soft and pliable. When dry, the lens becomes hard and brittle. These states are completely reversible and a lens which has been permitted to dry out will recover all of its hydrated properties when placed in normal saline for a period of two hours. When placed on the human cornea, the hydrated lens acts as a refracting medium to compensate spherical ametropias. The material has a refractive index of 1.43 and the lens has a visible light transmittance greater than 97%.

INDICATIONS

AOSOFT® Hydrophilic Contact Lenses are indicated for the correction of vision in persons with non-diseased eyes who have spherical ametropias, corneal astigmatism of 2.50 diopters or less and/or refractive astigmatism of 2.00 diopters or less.

CONTRAINDICATIONS

AOSOFT® Hydrophilic Contact Lenses are contraindicated in the presence of any of the following conditions: (1) Acute and subacute inflammation of the anterior segment of the eye. (2) Any eye disease which affects the cornea and conjunctiva. (3) Insufficiency of lacrimal secretion. (4) Corneal hypoesthesia. (5) Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses.

WARNINGS

Medications and Eye Drops: AOSOFT® Lenses must be stored in an appropriate solution when off the eyes, the type of solution being dependent on the system used for disinfection. When the lenses are disinfected with the thermal disinfection system, they may be stored *only* in LENSRINS® or BOIL n SOAK® Solution (sterile, buffered preserved saline solution). When lenses are disinfected with the chemical disinfection system, they may be stored *only* in FLEXSOL® Solution (sterile, isotonic buffered solution containing Adsorbobase—a water soluble polymeric vehicle—and preserved with thimerosal 0.001%, chlorhexidine 0.005% and edetate disodium 0.1%).

No ophthalmic solutions or medications, including hard contact lens solution, can be used by AOSOFT® Lens wearers prior to or while the lenses are in place on the eyes. Also, no solutions, including hard contact lens solutions, other than LENSRINS® or BOIL n SOAK® Solution or FLEXSOL® Solution may be used on AOSOFT® Lenses when they are off the eyes.

Since liquids and vapors may be absorbed by AOSOFT® Lenses, they should not be placed in the mouth for wetting, nor wiped with a cloth or tissue.

Abrasions and Infections: If a lens becomes less comfortable than it was when first placed on the wearer's cornea, the lens should be removed immediately and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present, or any abnormal eye condition is observed concurrently with lens wear, the lens should be removed immediately and a physician consulted.

Wearing Restrictions: AOSOFT® Hydrophilic Contact Lenses should not be worn while swimming, sleeping, or in the presence of irritating fumes or vapors.

Visual Blurring: If visual blurring occurs, the lens must be removed until the condition subsides.

Lens Sanitation: Patients must adhere to the recommended daily sanitary care procedures for AOSOFT® Hydrophilic Contact Lenses. Failure to follow this procedure may result in the development of serious ocular infections.

PRECAUTIONS

Storage: AOSOFT® Lenses may be stored *only* in the appropriate storage solution: LENSRINS® or BOIL n SOAK® Solution or FLEXSOL® Solution depending on disinfecting methods used. If left exposed to air, the lenses will dehydrate, become brittle and break readily. If a lens dehydrates, it should be soaked in either LENSRINS®, BOIL n SOAK® or FLEXSOL® Solution until it returns to a soft, supple state.

Cleaning and Disinfecting: AOSOFT® Lenses must be both cleaned and disinfected daily. Separate procedures and products are needed to clean and to disinfect. Two methods of disinfection, thermal or chemical, have been shown to be equally effective. The choice of disinfection system should be made in consultation with your eye care practitioner.

Cleaning: Daily cleaning is necessary to remove mucus and other deposits which may have accumulated on the lens surface. Each time the lenses are removed from the wearer's eyes, both surfaces of the lenses must be cleaned using several drops of PREFLEX® Cleaning Solution (sterile solution of a nonionic cleaner preserved with thimerosal 0.002% and edetate disodium 0.1%). Lenses must be cleaned before they are disinfected, as deposits on the lenses tend to harden and become more difficult to remove after the lenses are disinfected.

Disinfecting: AOSOFT® Lenses may be disinfected with either a thermal or chemical regimen. One method or the other must be selected, but not both. THE USER MUST NOT ALTERNATE BETWEEN METHODS.

Thermal Disinfection Method: AOSOFT® Lenses may be effectively disinfected after cleaning with PREFLEX® Cleaning Solution with use of the AOTHERM™ Heating Unit For Lens Disinfection and LENSRINS® or BOIL n SOAK® Solution. Fresh LENSRINS® or BOIL n SOAK® Solution must be used for daily storage of lenses or each time the lens is stored. The AOTHERM™ Heating Unit For Lens Disinfection requires distilled water. The AOSOFT® Lens Storage Containers must be emptied and filled with fresh LENSRINS® or BOIL n SOAK® Solution just prior to disinfecting the lenses.

Chemical Disinfection: Disinfection with PREFLEX® Cleaning Solution, FLEXSOL® Solution and NORMOL® Rinsing Solution (sterile isotonic saline solution preserved with thimerosal 0.001% and chlorhexidine 0.005%) has also been shown to be an effective disinfection system for daily care of AOSOFT® Lenses.

AOSOFT® Lenses must be cleaned and rinsed daily (or after wearing) with PREFLEX® Cleaning Solution and NORMOL® Rinsing Solution. The AOSOFT® Lens Storage Containers must be emptied and refilled with fresh FLEXSOL® Solution each time the lens is stored. Fresh FLEXSOL® Solution must be used daily for storage and disinfection.

WARNING: DO NOT MIX OR ALTERNATE THE DISINFECTION AND STORAGE SYSTEMS. FLEXSOL® SOLUTION SHOULD NOT BE USED WITH HEAT.

Hygiene: Before handling the lenses, hands must be washed, rinsed thoroughly and dried with a lint-free towel. Cosmetics, lotions, soaps, oil and hand creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the spray has settled.

Fluorescein: Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with LENSRINS® or BOIL n SOAK® and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein.

ADVERSE REACTIONS

Serious corneal damage may result from wearing lenses which may have soaked in hard contact lens solutions. Eye irritation may occur within a short time after putting on a hypotonic lens. Removal of the lens will relieve the irritation.

Very rarely a lens may adhere to an eye as a result of a patient sleeping with the lens on, or as a result of wearing a hypotonic lens. If a lens adheres for any reason, the patient may be instructed to apply a few drops of LENSRINS® or BOIL n SOAK® Solution (if using a thermal disinfection regimen) or ADAPETTES® Cleaning and Rewetting Solution (sterile, isotonic, buffered solution containing Adsorbobase and preserved with thimerosal 0.002% and edetate disodium 0.05%) (if using a chemical disinfection regimen), and wait until the lens moves freely before removing it.

Clinical studies indicate that corneal edema as manifested by symptoms such as rainbows or halos around light or visual blurring may occur if lenses are worn continuously for too long a time. Removal of the lenses and a rest period of at least one hour generally relieve these symptoms. If symptoms do not subside promptly, professional consultation should be obtained.

Excessive tearing, unusual eye secretions and photophobia are not normal; if these symptoms occur, the patient should be examined to determine their cause.

DOSAGE AND ADMINISTRATION

Fitting: Conventional methods of fitting contact lenses do not apply to AOSOFT® (tetrafilcon A) Hydrophilic Contact Lenses. For a detailed description of the fitting technique, refer to the Fitting Guide for AOSOFT® Hydrophilic Contact Lenses, copies of which are available from: American Optical Corp., Soft Contact Lens Div., Southbridge, MA 01550.

Wearing Schedule: There may be a tendency for the patient to overwear the lenses initially. Therefore, the importance of adhering to the following initial daily wearing schedule should be stressed to the patient.

Day	Wear Time *(hours)*	Rest Period *(hours)*	Wear Time *(hours)*
1	4	2	4
2	4	2	4
3	5	2	5
4	6	2	5
5	7	2	5
6	7	1	6
7	8	1	7
8	8	1	8
9	9	1	8
10-14	10	1	balance of
15	all waking hours		waking hours*

*lenses should never be worn 24 hours a day

Lens Care and Handling: Care must be taken on the initial visit to assure that the patient is supplied with an AOSOFT® Wearer's Kit and fully understands all care and handling instructions for the lenses. As with any contact lens, regular recall visits are necessary to assure patient health and compliance with instructions.

How Supplied: Each lens is supplied sterile in a glass vial containing 0.9% sodium chloride solution buffered with monobasic and dibasic sodium phosphates. The glass vial is marked with the Vault Number, Dioptric Power, and Lot Number.

The AOSOFT® Wearer's Kit is required for lens cleaning, disinfection and storing of the lenses. The Kit may consist of either of the following:

Thermal Disinfection Regimen: AOSOFT® Wearer's Kit, AOTHERM™ Heating Unit For Lens Disinfection, LENSRINS® Solution, PREFLEX® Cleaning Solution, AOSOFT® Wearer's "How To" Book, AOSOFT® Lens Storage Container.

Chemical Disinfection Regimen: AOSOFT® Wearer's Kit, AOSOFT® Lens Storage Container, PREFLEX® Cleaning Solution, NORMOL® Rinsing Solution, FLEXSOL® Storage and Disinfection Solution, AOSOFT® Wearer's "How To" Book.

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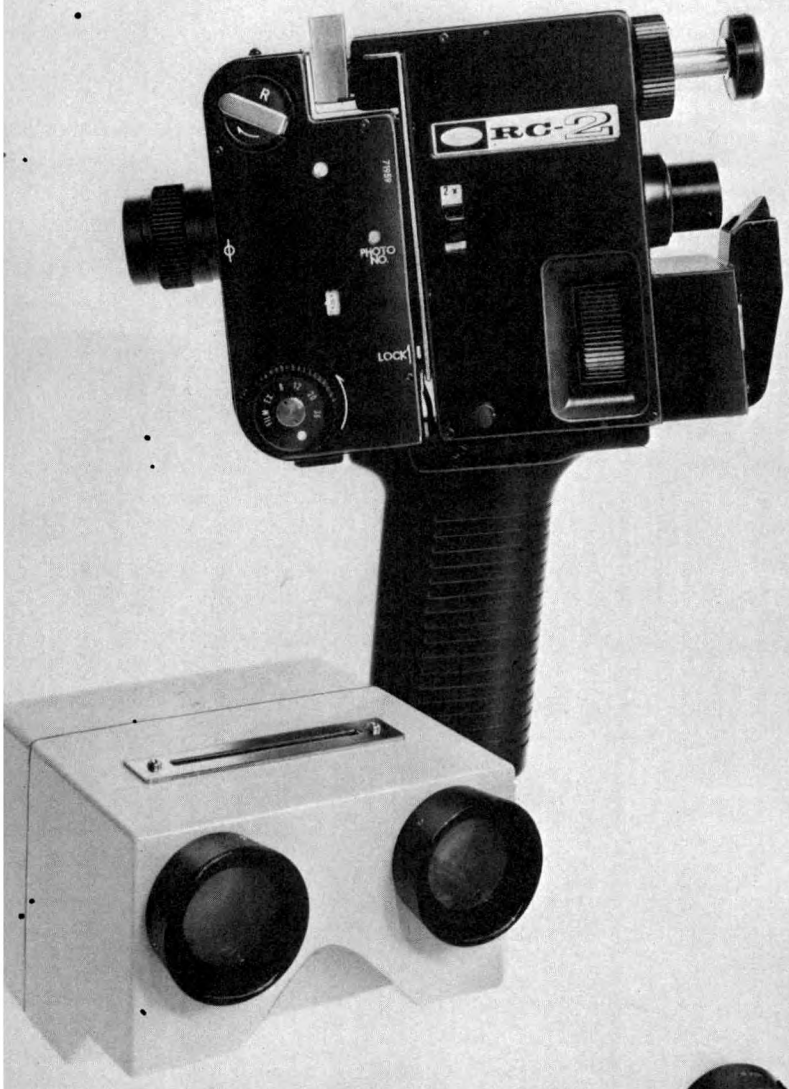
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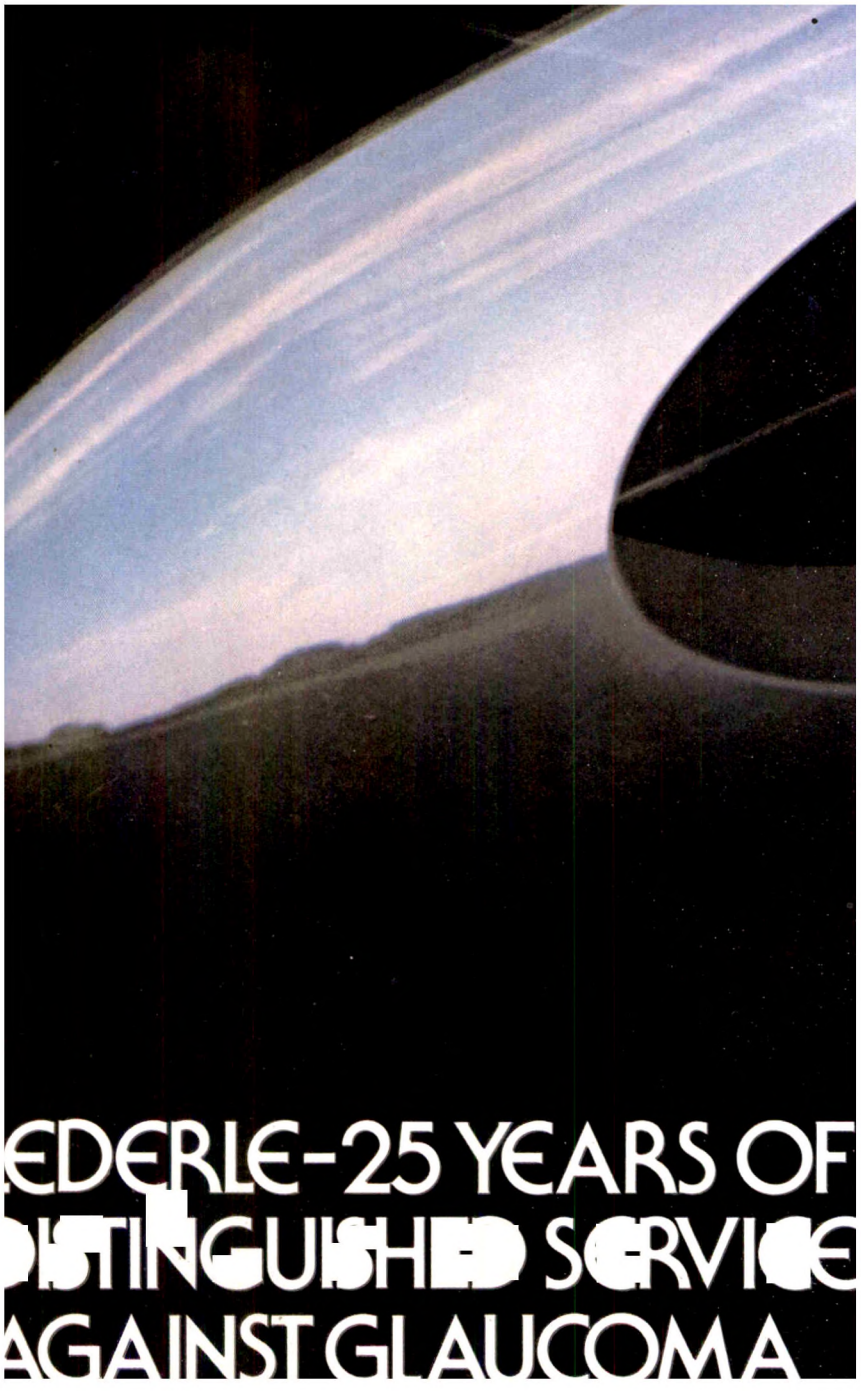
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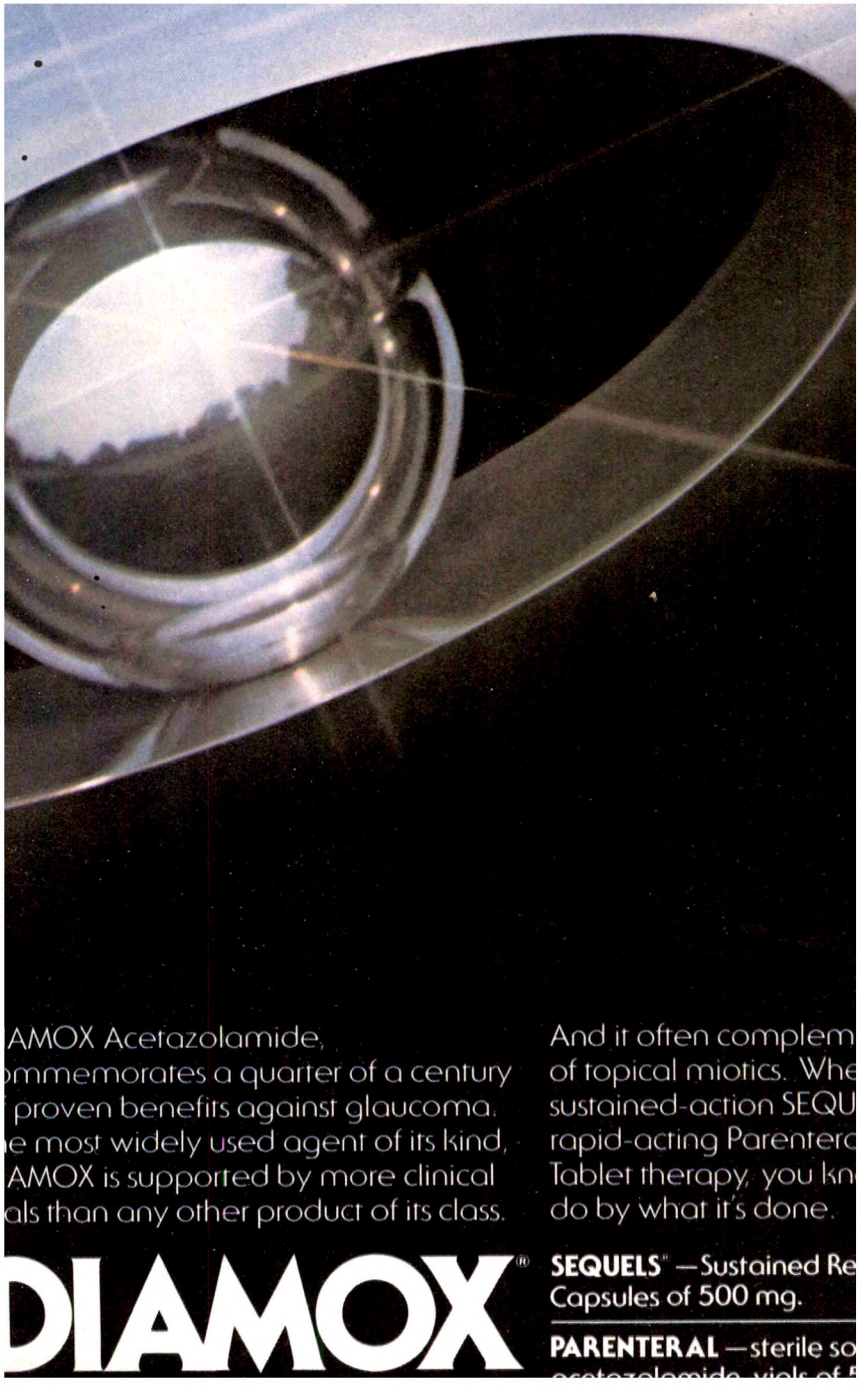
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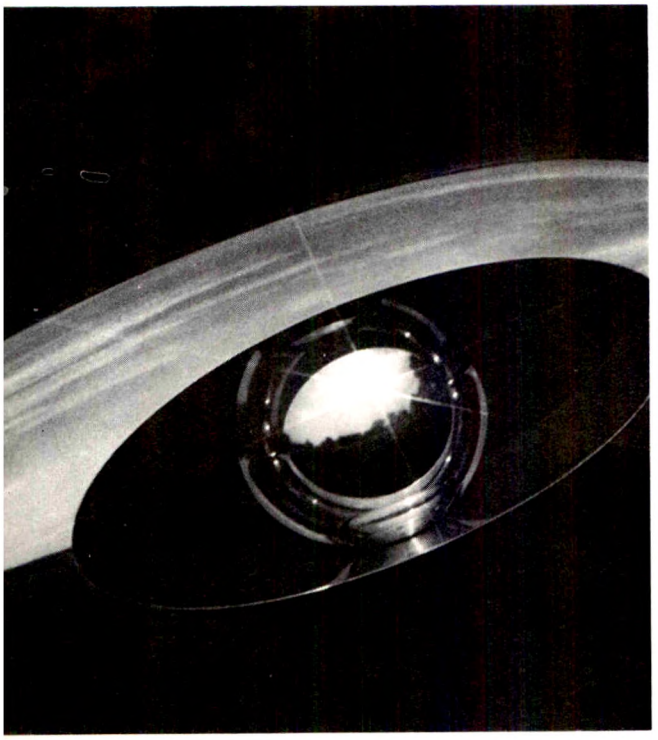
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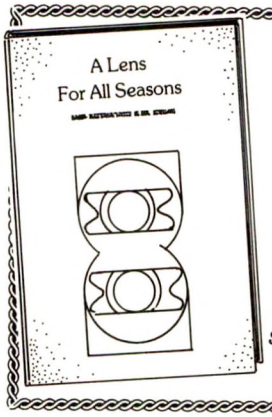
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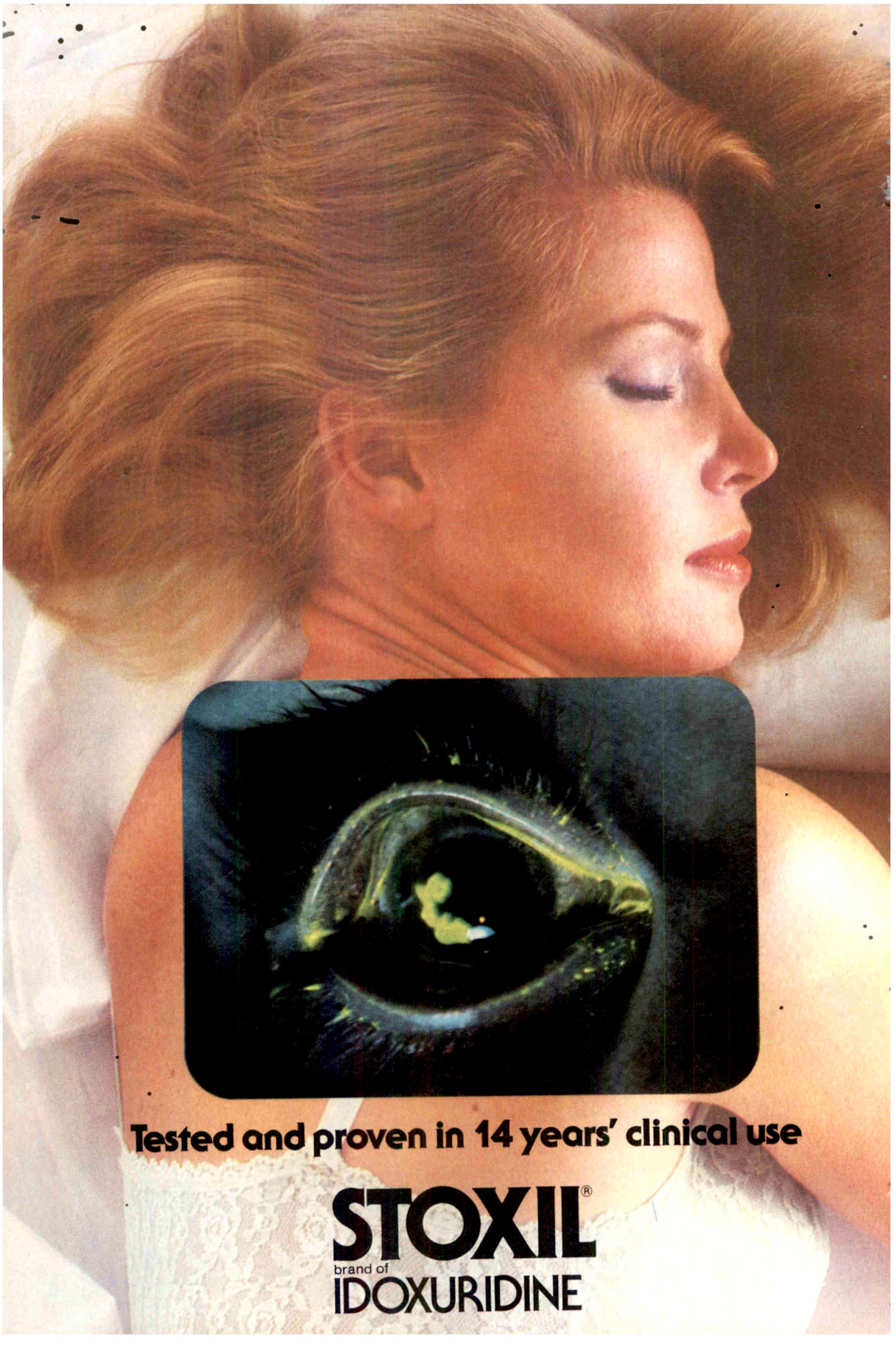
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INDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are indicated in the topical treatment of infections of the external eye and its adnexa caused by susceptible bacteria. Such infections embrace conjunctivitis, keratitis and keratoconjunctivitis, corneal ulcers, blepharitis and blepharoconjunctivitis, acute meibomianitis, and dacryocystitis.

CONTRAINDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are contraindicated in patients with known hypersensitivity to any of the components.

WARNINGS GARAMYCIN **Ophthalmic Solution** is not for injection. It should never be injected subconjunctivally, nor should it be directly introduced into the anterior chamber of the eye.

PRECAUTIONS Prolonged use of topical antibiotics may give rise to overgrowth of nonsusceptible organisms, such as fungi. Should this occur, or if irritation or hypersensitivity to any component of the drug develops, discontinue use of the preparation and institute appropriate therapy.

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ADVERSE REACTIONS Transient irritation has been reported with the use of GARAMYCIN **Ophthalmic Solution.**

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DOSAGE AND ADMINISTRATION GARAMYCIN **Ophthalmic Solution:** instill one or two drops into the affected eye every four hours. In severe infections, dosage may be increased to as much as two drops once every hour.

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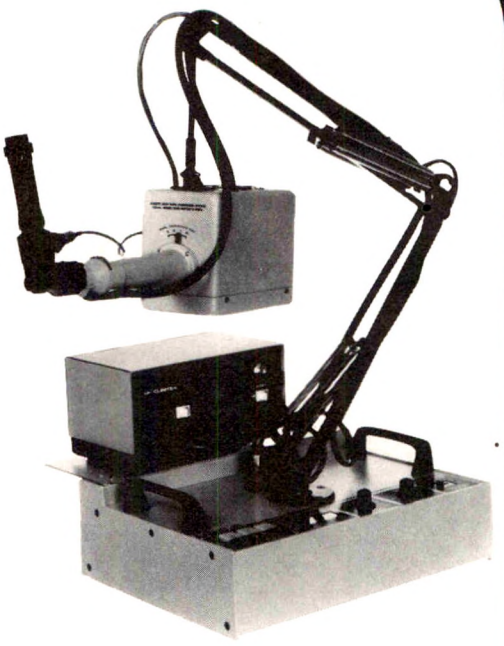
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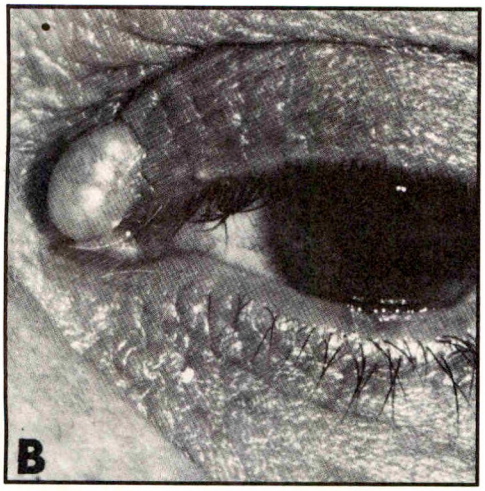
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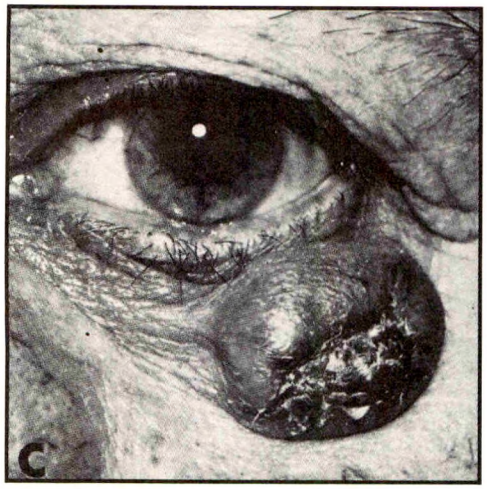
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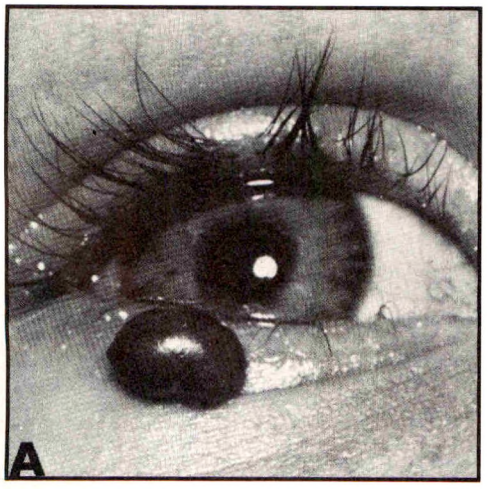
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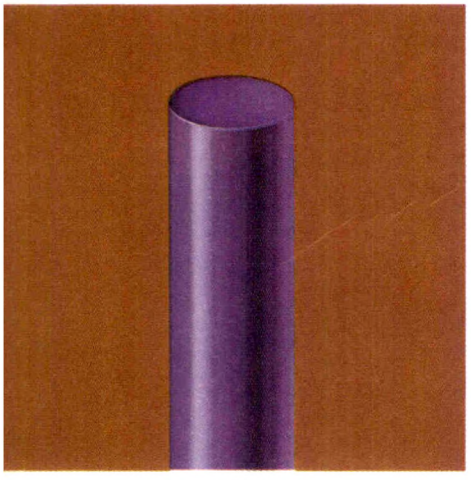
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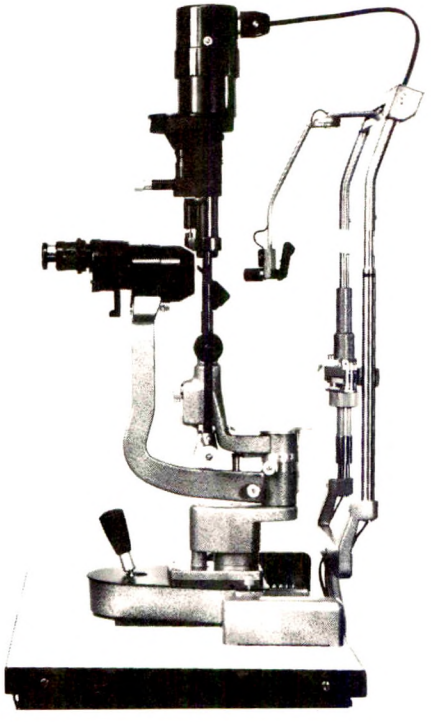
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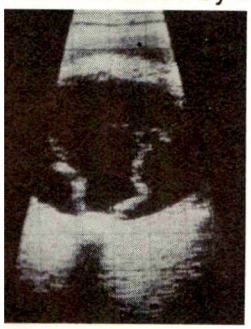
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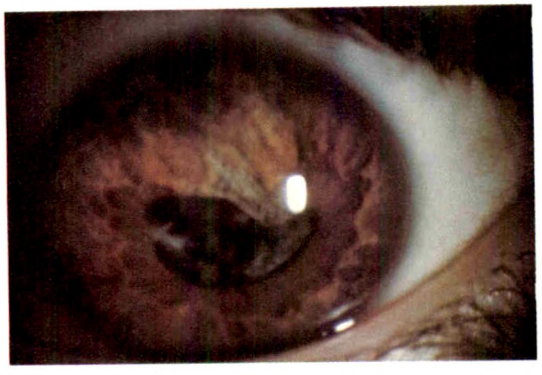
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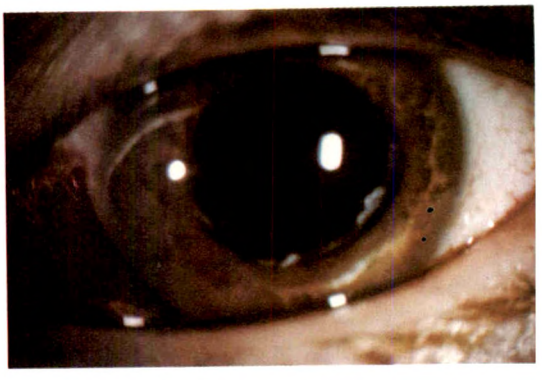
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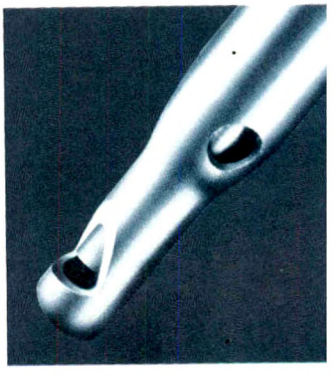
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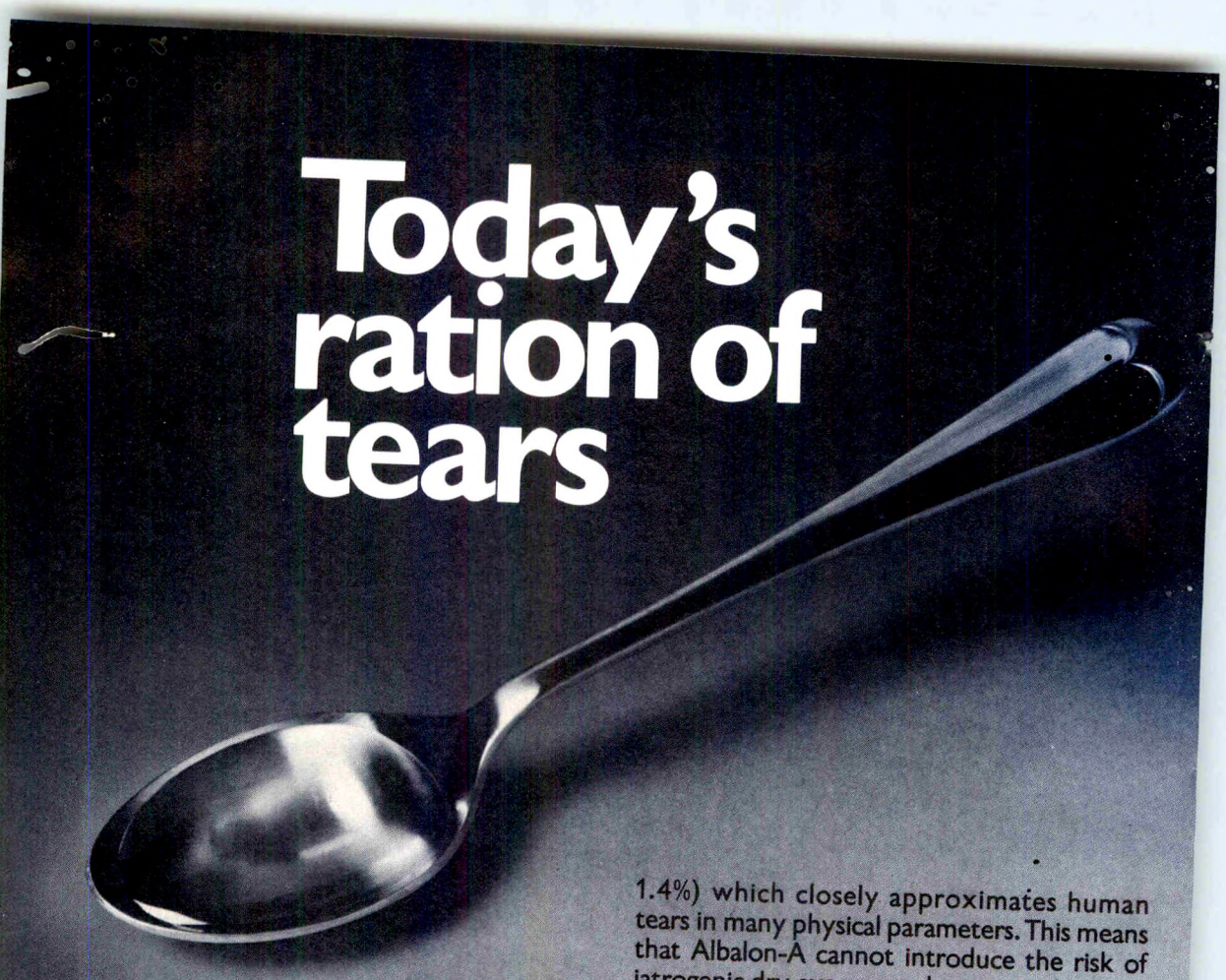
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1. Bennett, J. E. The management of total xerophthalmia. Arch Ophthal 81:667-682, 1969.

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RETAIL COST OF ANTIGLAUCOMA DRUGS IN TWO CITIES

ROBERT RITCH, M.D., NEWELL HARGETT, M.D., AND STEVEN PODOS, M.D.

New York, New York

AND

MICHAEL A. KASS, M.D., AND BERNARD BECKER, M.D.

St. Louis, Missouri

The question of possible monetary advantages to prescribing generic as opposed to brand-name drugs has been debated extensively in both the medical and the lay press. Although the cost benefit to the patient from the prescription of generic drugs has been cited often,[1–6] it has not been borne out in some studies.[7,8] The findings of differences in bioavailability and bioequivalence between different marketed forms of the same drug have further fueled the controversy.[9] Other studies have suggested that price may vary with the type[10–14] and locale[15,16] of the pharmacy and the number of services it offers.[17] Race, dress, and appearance of the patient have been considered important in some studies.[12,16]

Little information exists on the retail cost of ophthalmic medications. In a cost study of antiglaucoma medications in the St. Louis area, Kass and Becker[7] reported no statistically significant difference in price between medications prescribed by generic and brand names. The present study expands on the previous one to include another geographical area (New York City) to compare the results in St. Louis and Manhattan and to investigate the effect of the race of the patient on the cost of two drugs used to treat glaucoma.

METHODS

Two employees of the Department of Ophthalmology at the Mount Sinai School of Medicine volunteered to purchase antiglaucoma medications from pharmacies in Manhattan: a middle-aged white woman and a middle-aged, dark-skinned Hispanic woman. Although neither had glaucoma, both were familiar with the disease and the drugs studied. The Hispanic shopper pretended to know little English. To include diverse neighborhoods of the major ethnic groups and socioeconomic strata, 24 pharmacies were selected from the Manhattan telephone directory.

The two volunteers were given generic-name prescriptions for 15 ml of pilocarpine 4%, one drop to both eyes four

From the Departments of Ophthalmology, Mount Sinai School of Medicine of the City University of New York, (Drs. Ritch, Hargett, and Podos), New York; and Washington University School of Medicine, (Drs. Kass and Becker) St. Louis, Missouri. This study was supported in part by Grants EY 02514 and EY 00336 from the National Eye Institute, Bethesda, Maryland. Dr. Ritch was an NIH (EY 05128) and a Heed Foundation Fellow (1977–1978). Dr. Hargett was a Fight for Sight, Inc., New York, Fellow (research grant F-302, in honor of Elsie K. Sloate).

Reprint requests to Robert Ritch, M.D., Department of Ophthalmology, Mount Sinai Medical Center, One Gustave Levy Place, New York, NY 10029.

times a day; and 250 mg of acetazolamide No. 30, one tablet orally four times a day. The white volunteer returned to the same pharmacies one month later with brand-name prescriptions for 15 ml of Isoptocarpine 4%, one drop to both eyes four times a day; and 250 mg of Diamox No. 30, one tablet orally four times a day.

A middle-aged white woman with glaucoma visited 33 randomly chosen community pharmacies in the Missouri counties of St. Louis, Jefferson, and Franklin. The same prescriptions as above were used on the first visit, with half the pharmacies receiving brand-name prescriptions and the other half receiving generic prescriptions. The pattern was reversed on the second visit one month later.

In addition to purchasing the drugs, the shoppers noted: (1) any information requested by the pharmacy as to their general health or other medications used, (2) any advice given spontaneously regarding the drugs purchased, and (3) responses to a question concerning the spacing of doses of the drops.

All drugs were paid for in cash, and itemized receipts were collected. The drugs were checked as to manufacturer, correctness of contents, and labelling.

In St. Louis, information on a number of cost factors pertinent to the pharmacies and various services offered by the pharmacies was available from a state-wide study on cost-reimbursement for Medicaid by the St. Louis College of Pharmacy. The data from the Medicaid study were combined with our data in a masked way by using identification codes for each pharmacy to preserve the confidentiality of the information. Similar data were not available in Manhattan, and, as an alternative, a questionnaire was mailed to each of the pharmacies included in the study. One part of the questionnaire dealt with the brands of antiglaucoma medications stocked by the pharmacy and the reasons for stocking them. The other part requested information as to whether the pharmacy provided: (1) delivery, (2) 24-hour emergency service, (3) patient consultation with the pharmacist regarding physician instructions, (4) charge accounts, and (5) maintenance of patient medication profiles.

RESULTS

Data were complete for 22 pharmacies in Manhattan and 31 pharmacies in the St. Louis area. Two pharmacies in each area were dropped from the final tabulation because they failed to fill one prescription.

The total cost of either generic or brand-name drugs (white shopper) was significantly ($P<.02$, generic; $P<.005$, name brand) greater in Manhattan than in St. Louis (Table). All results were calculated on actual drug price and did not take into account the 6.5% sales tax on prescription drugs in St. Louis.

The prices for drugs prescribed generically and those for drugs prescribed by brand name for pilocarpine, acetazolamide, or the two combined did not differ significantly statistically in either Manhattan or St. Louis (Table).

In Manhattan, only three of 44 prescriptions for generic pilocarpine were actually filled with non-brand-name products. In 30 of 44 cases, Isoptocarpine was dispensed; Pilocar was dispensed in ten others. The mean costs of the drugs were as follows: Isoptocarpine, \$4.55; Pilocar, \$4.26; and three generics, \$2.88. Therefore, the difference in price of a generic prescription dispensed generically or as a brand-name drug was significant. (A formal statistical analysis was not carried out because of the small sample size.) In St. Louis, 23 of 31 generic prescriptions were filled with Isoptocarpine, six with Pilocar, and two with generic forms of pilocarpine. The mean cost of the drugs was as follows: Isoptocarpine, \$3.86; Pilocar, \$3.02; two generics, \$3.80.

All 44 generic prescriptions for acet-

TABLE

PATIENT COST FOR DRUGS USED TO TREAT GLAUCOMA: MEAN DOLLARS ± SD (RANGE)

Location (No. of Pharmacies)	Pilocarpine	Acetazolamide	Both
Manhattan (22)			
Brand name	4.46 ± 0.64* (3.39 – 5.45)	5.05 ± 0.90† (3.75 – 7.50)	9.51 ± 1.48* (7.15 – 12.45)
Generic			
White	4.29 ± 0.85† (2.25 – 5.45)	4.98 ± 1.02‡,§ (3.50 – 7.50)	9.27 ± 1.73†,§ (6.15 – 12.45)
Hispanic	4.45 ± 0.94 (2.50 – 5.95)	5.19 ± 1.12§ (3.30 – 8.65)	9.64 ± 1.79§ (6.75 – 13.15)
St. Louis Area (31)			
Brand name	3.84 ± 0.70* (2.82 – 5.30)	4.40 ± 0.91† (3.00 – 6.65)	8.22 ± 1.51* (6.02 – 11.95)
Generic	3.69 ± 0.83† (2.00 – 5.30)	4.43 ± 0.97‡ (2.70 – 6.65)	8.12 ± 1.67 (5.20 – 11.95)

Significant difference between Manhattan and St. Louis area, Student t-test:

* P<.005
† P<.02
‡ P<.05
§ Significant difference between white and Hispanic, paired t-test, P<.05.

azolamide in Manhattan were filled with Diamox. In St. Louis, 30 of 31 prescriptions were filled with Diamox, and only one was filled with a generic form of the drug.

Acetazolamide alone or in combination with pilocarpine was significantly (P<.05) more expensive for the Hispanic shopper (Table). Pilocarpine (generic prescription) was more expensive when purchased by the Hispanic shopper, although the difference in cost did not reach statistical significance. The Hispanic shopper paid more in 12 pharmacies, the white shopper in four, and the two paid equal prices in six pharmacies.

The 22 pharmacies in Manhattan were divided into two equal groups, those located in poorer neighborhoods and those in more affluent neighborhoods. There was no significant difference in the mean total price of all drugs in each pharmacy between the two groups of pharmacies ($28.46 for the "better" neighborhoods and $28.38 for the "poorer" neighborhoods). Prices for each category (white generic, white brand-name, Hispanic generic) were not significantly different between the two types of neighborhoods. There was no significant difference between the prices charged the white shopper comparing brand-name prescriptions with generic prescriptions in either the better or poorer neighborhoods. In the better neighborhoods, the mean price for the two drugs prescribed generically paid by the Hispanic shopper ($9.67 ± 2.14) was significantly (P<.05) greater than that paid by the white shopper ($9.20 ± 2.06). The difference in the poorer neighborhoods was not significant, but the white shopper paid less (Hispanic shopper: $9.61 ± 1.57; white shopper: $9.34 ± 1.52). In the stores in the better neighborhoods, the Hispanic shopper paid more in eight of 11 pharmacies, and the two shoppers were charged equally in the other three. In the stores in the poorer neighborhoods, the Hispanic shopper paid more in four, the white shopper paid

more in four, and the prices were equal in three. The number of pharmacies charging the Hispanic shopper more than the white shopper was not significantly greater in the better neighborhoods than in the poorer neighborhoods.

A twofold difference in price existed between the most and least expensive pharmacies with regard to total price of pilocarpine and acetazolamide in each category in each city. The lowest total price in Manhattan was $6.15 (white, generic), and the highest was $13.15 (Hispanic, generic). The lowest total price in St. Louis was $5.20 (generic), and the highest was $11.95 (both generic and brand).

In Manhattan, eight questionnaires designed to obtain information on customer services and to determine availability of generic drugs were returned after the first mailing, and six more were returned after the second. The remaining ten pharmacies were telephoned, and information was obtained from nine regarding services available.

In Manhattan, the six pharmacies offering four services charged the highest prices overall, but the costs to the patients were similar for all other pharmacies that offered from none to three services. There was a direct correlation between price and services offered in St. Louis area pharmacies.

All 14 Manhattan stores responding to the questionnaires stocked pilocarpine, epinephrine, acetazolamide, and echothiophate iodide in the commonly prescribed percentages. Most stocked carbachol, and less than half stocked demecarium bromide or eserine. In most cases, brand names only were stocked. The reasons given for stocking these particular brands included: (1) frequent prescription, (2) familiarily with the drugs, and (3) reliability of the company.

Six of the 14 respondents stated that they sometimes had difficulty interpreting prescriptions for eye medications. They generally complained about lack of specific instructions concerning the size of bottles to be dispensed and frequency of instillation. Two of the respondents indicated confusion with regard to "OD" meaning "right eye" or "daily."

Two errors were made in filling the 132 prescriptions in Manhattan (1.5%). One 30-ml bottle of pilocarpine was dispensed instead of a 15-ml bottle, and one bottle of acetazolamide was labelled "twice a day" instead of "four times a day." Four errors or difficulties were found in filling the 124 prescriptions in St. Louis (3.2%): (1) Diamox was not labelled by name on one prescription, (2) Diamox was labelled as 150 mg on one prescription, (3) one pharmacist did not know that acetazolamide was the generic name for Diamox until the shopper informed him, and (4) a prescription for acetazolamide was filled with the oral hypoglycemic agent acetohexamide, a potentially serious error.

In Manhattan, information regarding advice and questions was tabulated only for the white shopper purchasing the generically prescribed medications, as the Hispanic shopper pretended not to speak English well. Sixteen of 22 pharmacists requested the shopper's name and address, and six of these requested the correct spelling of the name of the physician. One asked if this were the first time she was using the medications. Five asked for no information at all. None of the pharmacists requested information as to any other medications the shopper might be using or any other illnesses she might have. Despite this, on the questionnaire, several of these pharmacies claimed to maintain patient medication profiles. Eleven of the 22 pharmacists voluntarily explained the labels on the bottles and gave instructions as to the use of the drops, or both. Eight more pharmacists were able to answer the question concerning the timing of the drops, whereas three

could not or would not give any information at all.

In St. Louis, 47% of the pharmacies claimed to maintain complete patient medication profiles, but only 14% asked any questions pertinent to this. All of the pharmacies claimed to consult with patients regarding physicians' instructions, but only 34% offered any spontaneous advice. Seventy-seven percent of the St. Louis pharmacies were able to answer the question concerning the timing of the drops.

Discussion

Generic vs brand name prices—In the United States most prescriptions are written for brand-name items.[18] Some studies found generically prescribed drugs to be less expensive than those prescribed by brand name,[1-6] whereas others found no[7] or little[8] difference. The results obtained in both cities in our study indicate no significant price difference between antiglaucoma drugs prescribed according to generic and brand names.

However, the majority of the generic prescriptions were filled with brand-name items. Although only a few prescriptions were filled with generic forms of the drugs, the results from the Manhattan purchases suggest that generic prescriptions are less expensive when filled with generic forms of the drug. Similar results were found by Azornoff[1] in a study of the retail cost of meprobamate. In the St. Louis area, the few generically filled prescriptions were intermediate in price between the two common brands of pilocarpine dispensed, whereas the one prescription for acetazolamide filled with a generic product was the least expensive of all ($2.70). The Drug Topics Red Book[19] lists one of the brands of pilocarpine (Pilocar) as less expensive than a number of generically dispensed items, whereas another brand (Isoptocarpine) is more expensive than all but one generic form. Diamox is more expensive than all generic forms of acetazolamide listed.

Pharmacists often fill generic prescriptions with brand items with which they are more familiar—an important determinant of availability of the drugs. Horvitz[4] stated:

> Pharmacists who were better informed as to which drugs were available generically were more likely to stock alternative products and more likely to charge lower prices on generic prescriptions than on brand name prescriptions.

Apparently, a prescription specifying the generic form of the drug is cheaper when filled with the generic form. Kemp and Moyer[5] suggested writing the generic form and the manufacturer of the lowest priced therapeutically equivalent product on the prescription. However, physicians have overestimated[13] and underestimated[20] drug prices. Generally, physicians are not familiar with the Drug Topics Red Book or the American Druggist Blue Book.[21]

The wholesale cost of a drug is only one factor in the final price.[22] Some authors found that prices varied according to the type of store[10,12,13] or hospital.[11,14] In St. Louis, prices were not significantly lower at chain stores or at stores with lower operating expenses or lower costs per prescription, although there was a trend in these directions. Few chain stores exist in Manhattan. Chain stores that advertise discount prices are not necessarily cheaper,[13] and deviations occur in the prices of the same prescriptions within a given pharmacy over a period of time.[23]

Location—Prices in Manhattan were uniformly higher than those in St. Louis. No difference was found in prices charged by pharmacies between better and poorer neighborhoods in Manhattan, nor was any difference found in the St. Louis area in urban, suburban, or rural pharmacies. Other studies found higher prices in small towns[15] and suburban areas.[16]

Race—In our study, the Hispanic shop-

per paid a significantly higher price overall than did the white shopper. The price differential was greater in better neighborhoods, but the white shopper paid less in poorer neighborhoods as well. In contrast, Braucher and Kotzan[10] and Hayes and Whalley[24] found no difference in price with regard to race or dress of the shopper. Hayes and Whalley[24] also found no difference in the costs for male and female shoppers. Hastings and Kunnes[12] found prices to vary with store type for both white and black customers, and found blacks paying more than whites only in independent, variety-type pharmacies in poor neighborhoods with few nearby competitors. However, Weinstein[16] found blacks to be charged more than whites. The findings in Manhattan corroborate the studies that indicate nonwhites may be charged more than whites in certain types of stores or locations.

Price range—Other studies[11,16,24] also found a greater than twofold price range for the drugs purchased. The price differential to the patient who shops carefully can be extraordinary. Using the figures from the Manhattan acetazolamide purchases alone, the extremes are $3.30 and $8.65. A patient on a full regimen of acetazolamide takes 1,460 tablets per year. At the previously mentioned rates, a potential saving of over $260 could be obtained on the acetazolamide alone by careful comparison shopping.

Errors—The percentage of errors made in filling the prescriptions in both Manhattan (1.5%) and St. Louis (3.2%) is similar to that found in other studies.[24,25] Wertheimer[23] found a 9.8% error rate, which included omission of the drug name from the label. In the series of Fleckenstein, Horvitz, and Morgan,[25] six of 232 prescriptions (2.6%) had directions for use other than those intended by the prescribers, two (0.9%) were errors made by the pharmacies, and four (1.7%) were errors in directions made by the physician in writing the prescriptions. This was borne out by a large number (43%) of the respondents to our questionnaire, who stated that they had trouble with ophthalmic prescriptions. In our study, most of the errors were minor, but one was a potentially serious substitution (acetohexamide for acetazolamide), which was previously reported.[26]

Costs and services—The number of services offered by the pharmacies corresponded to the mean costs of all drugs studied in the St. Louis area. The information on services was not directly available in Manhattan, and we had to rely on questionnaires and telephone information, which was perhaps not always accurate.[24] In a study of prescription price mark-ups, Gagnon and Rodowskas[17] found a positive correlation with the presence of delivery service. Jackson and Smith,[27] however, found no relation between price and quality of pharmaceutical services. Several pharmacies in Manhattan and St. Louis claimed to maintain patient medication profiles, but in few cases was the shopper questioned as to other medications she might possibly be taking. Rowles and Wertheimer[15] found only 20% of pharmacies offering advice at the time of dispensation of the drugs. In Manhattan, 50%, and in St. Louis, 34% of pharmacies offered advice on use of medications.

The results of this study suggest that physicians should be familiar with various forms and prices of available medications. The American Druggist Blue Book and Drug Topics Red Book are helpful references. Pharmacies should be encouraged to use generic equivalents when studies indicate bioequivalence. Easier access to such studies, perhaps in newsletter form, would benefit both pharmacists and physicians. Pharmacists should also be encouraged to maintain patient profiles for regular customers and to reinforce physicians' instructions. Patients should be urged to comparison shop for lower prices. Generically prescribed

drugs are not necessarily less expensive if they are only on the prescription and not in the patient's shopping bag.

SUMMARY

Volunteer shoppers purchased antiglaucoma medications dispensed from prescriptions written according to generic and brand-name products in Manhattan and in the St. Louis area. All drugs obtained were more expensive in Manhattan than in St. Louis. No significant cost difference was found between generic and brand-name items in either city, but only in a few instances were generic drugs actually dispensed. No difference in overall price was found between pharmacies located in better and poorer neighborhoods in Manhattan or between pharmacies located in urban, suburban, or rural areas in St. Louis. A white shopper paid significantly lower retail prices than did a Hispanic shopper in Manhattan, particularly in better neighborhoods. The range of prices in each city for all drugs studied was greater than twofold. Pharmacies offering more patient services tended to charge higher prices, but frequently, pharmacies did not actually offer the services they advertised.

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CLINICAL TRIAL COMPARING TIMOLOL OPHTHALMIC SOLUTION TO PILOCARPINE IN OPEN-ANGLE GLAUCOMA

WILLIAM P. BOGER III, M.D., ROGER F. STEINERT, M.D.,
CARMEN A. PULIAFITO, AND DEBORAH PAVAN-LANGSTON, M.D.
Boston, Massachusetts

In 1970, Hall and associates[1] described a new beta-adrenergic blocking agent, timolol. It is nonselective in that it blocks both $beta_1$ and $beta_2$ receptors. Unlike some other beta-blocking agents,[2] timolol has neither sympathomimetic effects nor local anesthetic properties. Although the β-adrenergic blocking agent propranolol was shown to decrease intraocular pressure (IOP) as early as 1967,[3] its mild anesthetic properties have made many investigators reluctant to use it as a topical medication for glaucoma. The absence of local anesthetic activity appears to make timolol a more reasonable choice for local use in long-term therapy. In animal experiments,[1,4] timolol has a beta-blocking potency five to ten times greater than that of propranolol. Timolol is formulated for clinical use as the levo isomer,[5] whereas propranolol is supplied as a racemic mixture. The levo isomer of timolol[6] and propranolol are more potent beta-blocking agents than the racemic mixtures. No unusual side effects have been reported from the short-term use of oral timolol. The oral use of timolol (Blockadren) as an antihypertensive agent was reported in 1971.[6] Several subsequent studies have demonstrated favorable results in the treatment of systemic hypertension and a beta-blocking potency greater than propranolol.[6–18]

Katz and associates[19] reported single-eyedrop studies using 0.5%, 1.0%, and 1.5% timolol ophthalmic solution in 15 normal volunteers. Intraocular pressures were decreased significantly when compared to 15 controls. Maximum effect was observed at one or two hours after administration and lasted at least seven hours. No side effects were observed; in particular, there was no ocular irritation, no alteration in pupillary size, and no change in visual acuity. Blood pressure and pulse rate were unaffected by the drops. Zimmerman and Kaufman[20] conducted a single-eyedrop study on 30 patients with glaucoma and found significant lowering of IOP with timolol eyedrops. A 50% reduction in the IOP was obtained when pressure readings at seven hours after the eyedrops were compared with pretreatment levels. They also noted a lesser but significant decrease in the IOP of the untreated fellow eye. Pulse rate and blood pressure did not appear to be affected. Patients tolerated the drops well and the pupil was unaffected. Zimmerman and Kaufman[21] conducted a dose response analysis to a single eyedrop in 20 glaucoma patients. They concluded that maximum effect was achieved by a concentration of 0.5%. They also noticed a prolonged duration of action, still present at least 24 hours after the eyedrop. Tonography was performed by Zimmerman and associates[22] before and after single doses of timolol and placebo in a double-masked randomized study. A small increase in mean facility of outflow after timolol was not statistically significant, $P < .1$.

This current study was designed to compare timolol to pilocarpine in the

From the Massachusetts Eye and Ear Infirmary, Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts. It was supported in part by a grant from Merck, Sharp and Dohme Research Laboratories, West Point, Pennsylvania.

Reprint requests to William P. Boger, III, M. D., Children's Hospital Medical Center, 300 Longwood Ave., Boston, MA 02115.

treatment of open-angle glaucoma over a ten-week maintenance period. A double-masked, randomized protocol was used.

SUBJECTS AND METHODS

The criterion for admission to the study was open-angle glaucoma requiring therapy. All patients entered had an IOP greater than 21 mm Hg without medication. Patients with ocular inflammation, recent ocular surgery or trauma, asthma or chronic obstructive pulmonary disease, congestive heart failure, bradycardia (defined as a resting pulse of 56 beats per minute or less), as well as pregnant or nursing women, and children were excluded from the study. Informed consent was obtained from all patients before entry.

Patients stopped taking their previous antiglaucoma medications and were treated with placebo eyedrops, three times daily for one week, after which time we performed the baseline examination. The one-week therapy-free interval was shortened if the investigator regarded the increased IOP as dangerous for the patient. Once the washout period and baseline examinations were completed, the patient entered a titration period. For each patient in the study, three boxes containing vials of eyedrops had been prepared and labelled. For example, patient No. 1, vial A: patient No. 1, vial B; and patient No. 1, vial C. Both the patient and the investigator knew that vial A contained either pilocarpine 2% or timolol 0.25%. They also knew that if vial A for that particular patient happened to be pilocarpine, then vial B would contain 3% pilocarpine and vial C would contain 4% pilocarpine. On the other hand, if vial A had contained timolol, then vial B would contain timolol 0.50% and vial C would contain timolol 1.0%. In other words, the three boxes of eye dropper vials were matched for each patient, so that he would receive in sequence, either timolol 0.25%, timolol 0.50%, and timolol 1.0% or pilocarpine 2%, pilocarpine 3%, and pilocarpine 4%. In packaging the vials, timolol or pilocarpine had been assigned to patient numbers in a randomized fashion. The code revealing which patient numbers had been given timolol and which had received pilocarpine was retained by the manufacturer who had packaged the vials. The pilocarpine and timolol vials and solutions were indistinguishable to the investigators and patients. The investigator titrated the patients and then conducted the ten-week maintenance portion of the study without knowing whether the patient was receiving timolol or pilocarpine. A given patient received only timolol or pilocarpine during the course of the study. Once the patient completed the titration and ten-week maintenance period, the code was broken by calling the manufacturer. The code could also be broken if an adverse reaction occurred.

After the baseline examination, the titration period was initiated with vial A, one eyedrop three times daily. A follow-up examination was performed in one week. If the IOP was controlled (defined in this study as an IOP $\leqq$ 21 mm Hg on two separate readings at least one hour apart), the patient continued with vial A and entered the maintenance phase of the study. If, on the other hand, the IOP was 22 mm Hg or greater, the investigator instilled an eyedrop of the test vial into the patient's eye and checked the IOP one hour later. This was done to control for patient compliance and excessive intervals after the last application of medication. If the IOP was improved an hour later, this patient was instructed to instill the medication within one to two hours of each future examination. If the IOP still was not 21 mm Hg or less with vial A, treatment with vial B, one eyedrop three times daily, was begun. The patient was asked to return in one week. If the pressure was now $\leqq$ 21 mm Hg or less on two

separate measurements on the same day, the patient continued using vial B and entered the maintenance phase of the study. If the IOP was still ≧ 22 mm Hg on either reading, treatment with vial C, one eyedrop three times daily, was begun. If the patient had an IOP > 21 mm Hg after treatment with vial C for one week, he was discontinued from the study unless the investigator thought there was a satisfactory response for that particular patient's condition.

Once the patient was titrated to a satisfactory IOP with vial A, vial B, or vial C, he entered the maintenance phase of the study. For the maintenance phase he continued using the same vial, one eyedrop three times daily, and returned for examination two weeks, six weeks, and ten weeks after titration. If the patient was using vial A or vial B and had an IOP ≧ 22 mm Hg during the maintenance period, he was retitrated and subsequently started another ten-week maintenance period. Patients using vial C who had an IOP ≧ 22 mm Hg continued in the ten-week maintenance period only if the IOP was considered satisfactory for the status of the glaucoma.

The baseline examination and each subsequent examination consisted of the following: visual acuity; applanation tonometry; examination of the cornea, conjunctiva, eyelids, and lens with the slit-lamp biomicroscope; examination of cornea and conjunctiva after application of 1% rose bengal; measurement of tear production using the Schirmer test strip; measurement of pupil size; and direct or indirect ophthalmoscopic examination, or both. Two applanation pressure readings were taken with an interval of at least one hour between the two measurements. The examinations were conducted at approximately the same time of day at each visit. Tonography was performed by one investigator using the same instrument at the baseline examination and was repeated during the maintenance phase at the six-week and ten-week examinations. Visual fields were recorded by means of the Goldmann perimeter at the baseline examination and at the conclusion of the study, the ten-week examination of the maintenance phase.

At each examination, the pulse was measured for 60 seconds after the patient had been seated for at least four minutes. Blood pressure was taken with the patient seated and using the same arm for each measurement. Subjective symptoms were quantitated on a scale of zero to three with specific questioning about burning, tearing, smarting, dryness of the eyes, foreign body sensation, itching, photophobia, soreness of the eyes, eye ache or tiredness, brow ache, headache, blurred vision, or other.

RESULTS

We recorded the pretreatment characteristics of the patients (Table 1). The group receiving pilocarpine contained a higher proportion of men, blacks, dark brown irides, patients with visual field abnormalities, and patients who were receiving maximal or near-maximal medical therapy. The visual field abnormalities were generalized constriction or enlargement of the blind spot; no eye in either group exhibited scotomata or a nasal step. The two groups had nearly identical mean baseline applanation pressures and mean facilities of outflow.

Patients receiving timolol experienced a mean fall in IOP at least as large as did patients receiving pilocarpine (Fig. 1). According to a Student's *t*-test comparison, timolol decreased IOP more than pilocarpine at a significance level < .10. The mean IOP of the patients entering the timolol and pilocarpine groups were nearly identical (Table 1). We plotted factors determined in adequately controlled patients over the ten-week maintenance period (Figs. 2–4). A significant

TABLE 1

PRETREATMENT PATIENT CHARACTERISTICS

	All Patients	Timolol Group	Pilocarpine Group
No. of patients entered	28	13	15
No. of eyes entered	51	25	26
Mean age	56	56	56
Mean weight (lbs)	149	141	156
Sex ratio (male:female)	16:12	6:7	10:5
Black/white/other	6/21/1	2/10/1	4/11/0
Dark iris/light iris/blue iris	11/7/10	4/2/7	7/5/3
Prestudy glaucoma medications			
Pilocarpine or epinephrine alone	10	6	4
Pilocarpine and epinephrine	8	3	5
Carbonic anhydrase inhibitor or anticholinesterase or both	9	3	6
Mean baseline applanation pressure	33	34	33
Mean baseline facility of outflow	0.14	0.13	0.14
Optic nerve abnormalities (eyes)	27	12	15
Visual field abnormalities (eyes)	10	2	8

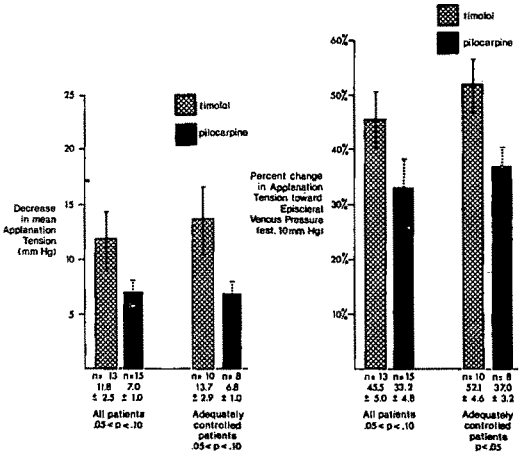


Fig. 1 (Boger and associates). Difference in IOP between untreated baseline value and the last available pressure on treatment. For adequately controlled patients, the treatment IOP is the ten-week value. For patients not adequately controlled, the difference was taken between the baseline and the last measurement before discontinuing the study. "All patients" includes adequately controlled patients and those who discontinued the study. Left, Results expressed as absolute decrease in applanation pressure in mm Hg. Right, Results expressed as percentage change toward episcleral venous pressure, assumed to be 10 mm Hg.

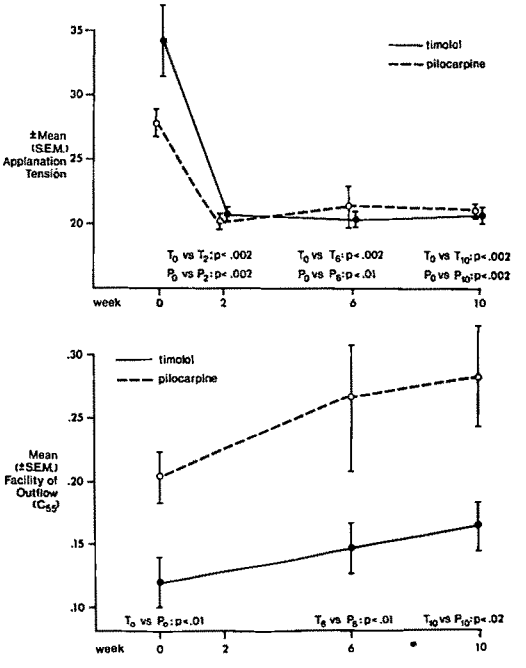


Fig. 2 (Boger and associates). IOP (top) and facility of outflow (bottom) at baseline and at two, six, and ten weeks into the maintenance period. Results of statistical analysis are displayed above the abscissa where P represents pilocarpine; T, timolol; and the subscript denotes the time interval. Differences are not significant unless indicated.

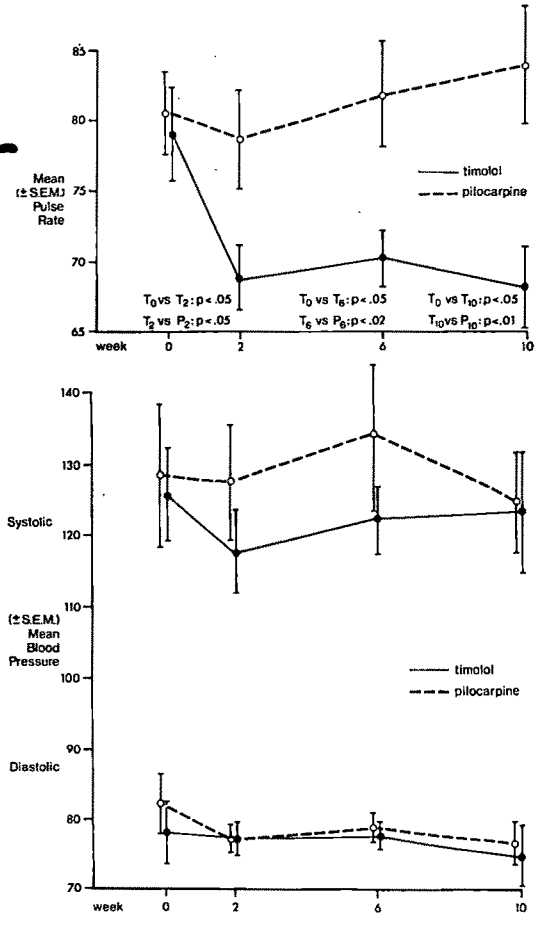


Fig. 3 (Boger and associates). Pulse rate (top) and blood pressure (bottom) at baseline and at two, six, and ten weeks into the maintenance period for adequately controlled patients. Results of statistical analysis are displayed above the abscissa where P represents pilocarpine; T, timolol; and the subscript denotes the time interval. Differences are not significant unless indicated.

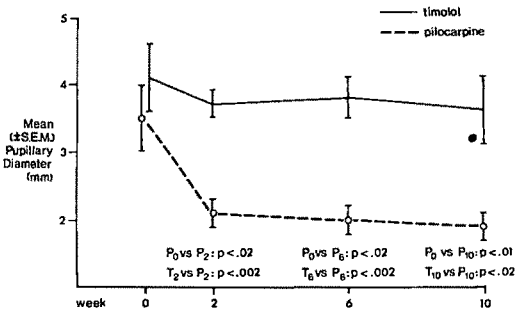


Fig. 4 (Boger and associates). Pupillary diameter at baseline and at two, six, and ten weeks into the maintenance period for adequately controlled patients. Results of statistical analysis are displayed above the abscissa where P represents pilocarpine; T, timolol; and the subscript denotes the time interval. Differences are not significant unless indicated.

decrease in IOP persisted through the ten weeks of the maintenance period (Fig. 2, top). Two of the ten patients who initially entered the maintenance phase while taking timolol were retitrated to a higher concentration and then completed a subsequent ten-week maintenance period. One of the eight patients who entered the maintenance phase while taking pilocarpine required retitration to a higher concentration, and he subsequently completed a ten-week maintenance period.

The mean facility of outflow tended to increase with pilocarpine and with timolol (Fig. 2, bottom). There was great variability in the tonography data and these trends, even for pilocarpine, do not reach statistical significance. The mean facility of outflow was significantly greater for adequately controlled patients receiving pilocarpine than for the timolol group at baseline and at weeks 6 and 10 of the maintenance period. The mean facility of outflow of the patients entering the timolol group was nearly identical to that of the pilocarpine group (Table 1). In other words, only patients with relatively good facilities of outflow responded adequately to pilocarpine. In contrast, the mean baseline facility of outflow of the patients controlled on timolol is the same as that of the population entering the study (Table 2).

The timolol group had a significant decrease in mean pulse rate (Fig. 3, top), which remained consistently depressed throughout the maintenance period, but the blood pressure did not change significantly (Fig. 3, bottom) and the patients did not report symptoms of light-

TABLE 2

SUMMARIZED PATIENT DATA AT BASELINE, TWO, SIX, AND TEN WEEKS

Patient No.	Age (yrs)	Prestudy Therapy*	Applanation Pressure R.E. (wks) 0	2	6	10	Applanation Pressure L.E. (wks) 0	2	6	10	Facility of Outflow (C_{55}) R.E. (wks) 0	6	10	Facility of Outflow (C_{55}) L.E. (wks) 0	6	10	Outcome†	Concentration of Medication at 10 Wks (%)
Timolol Group																		
1	55	E1; P1	27	23	—	—	27	24	—	—	.18	—	—	.16	—	—	3	—
4	72	P2	30	24	23	22	30	20	23	22	.12	.15	.18	.18	.22	.13	1	1
7	74	P2	24	22	21	—	31	22	21	—	.15	.11	—	.10	.20	—	1‡	1
8	26	None	45	20	21	24	47	21	21	24	.05	.13	.12	.06	.07	.10	1	1
10	45	E1; P4; EI; CAI	41	19	20	19	58	20	19	18	.03	.14	.11	.02	.07	.07	1	1
13	61	E1	28	18	20	20	29	18	20	20	.22	.19	.30	.12	.23	.22	1	1/4
14	61	E1; EI	28	27	—	—	32	27	—	—	.15	—	—	.15	—	—	2	—
16	55	E1	48	22	19	20	44	23	18	20	.05	.13	.11	.05	.12	.09	1	1
18	53	P1	30	20	21	22	31	20	21	22	.12	.10	.17	.12	.07	.18	1	1
19	53	E1; P4; EI	34	—	—	—	40	—	—	—	.23	—	—	.10	—	—	2	—
20	42	E1; P2 OD	29	19	18	20	—	—	—	—	.14	.21	.28	—	—	—	1	1/4
22	61	E1; P2	29	19	18	19	32	22	20	21	.14	.10	.10	.17	.07	.13	1	1/4
26	73	P2	27	22	22	20	26	24	24	21	.20	.17	.16	.22	.22	.21	1	1
Pilocarpine Group																		
2	57	P6; EI; CAI	44	—	—	—	50	—	—	—	.08	—	—	.04	—	—	2	—
3	61	P4; E2; EI; CAI	35	—	—	—	34	—	—	—	.10	—	—	.07	—	—	2	—
5	57	P2	32	20	21	22	31	20	18	21	.18	.26	.29	.15	.15	.33	1	4
6	62	E2; EI; CAI	49	—	—	—	39	—	—	—	.06	—	—	.11	—	—	2	—
9	49	E1; P4; EI	24	22	—	—	30	22	—	—	.12	—	—	.09	—	—	3	—
11	74	P4 OD	28	21	25	23	—	—	—	—	.15	.23	.15	—	—	—	1	4
12	40	E1; P2; CAI	25	20	21	20	25	20	19	19	.25	.30	.28	.27	.37	.29	1	4
15	64	E1; P1	27	19	21	20	28	19	20	21	.35	.52	.46	.26	.49	.53	1	2
17	66	C3; E; EI; CAI	49	—	—	—	46	—	—	—	.02	—	—	.05	—	—	2	—
21	43	E2; P2	32	23	27	19	33	24	34	22	.18	.29	.29	.15	.28	.26	1	4
23	37	E1	24	20	19	21	26	21	21	22	.19	.18	.21	.28	.28	.33	1	2
24	64	E1; P4	29	19	18	20	27	19	21	23	.27	.13	.25	.15	.26	.18	1	2
25	69	P2 OS	—	—	—	—	26	19	16	20	—	—	—	.14	.15	.25	1	2
27	60	P4; E2 OS	—	—	—	—	38	—	—	—	—	—	—	.06	—	—	3	2
28	36	P2 OD; E1 OS	29	—	—	—	—	—	—	—	.05	—	—	—	—	—	3	—

*E designates epinephrine; P, pilocarpine; C, carbachol; EI, echothiophate iodide; CAI, carbonic anhydrase inhibitor.
†1 designates adequate control; 2, inadequate control; 3, withdrew.
‡Adequate control, but terminated at 6 weeks when code was inadvertently broken.

headedness, dizziness, weakness, falling, or loss of consciousness. The pilocarpine group experienced a significant decrease in mean pupillary diameter, whereas that of the timolol group remained unchanged (Fig. 4).

There were no changes in the slit-lamp examination, including rose bengal staining, and no changes in direct and indirect ophthalmolscopy of the optic disk and retina. Visual field examinations were also unchanged. Schirmer values, while variable, did not show any consistent individual or group changes. Inconvenient symptoms encountered during the study were recorded. Timolol 1% solution was associated with a substantial increase in complaints of burning, stinging, or smarting briefly after instillation of an eyedrop compared to the weaker concentrations of timolol or to pilocarpine (Table 3). Brow ache and headache relating to the administration of medication occurred just once, in a patient receiving pilocarpine 2%. Only one patient in the timolol group reported altered visual acuity; review of the record indicated that use of miotics in the prestudy period had compensated for his age-appropriate presbyopia. In contrast, seven patients complained of decreased visual acuity or "darkening" of vision related to the administration of pilocarpine eyedrops. Two patients (one with cataracts) found this visual disturbance to be intolerable and were dropped from the study. Manifest visual acuity in patients complaining of altered vision ranged from no change to a decrease of three lines on a Snellen chart.

In addition to the two patients dropped from the study because of pilocarpine-induced visual impairment, two other patients were dropped for reasons other than failure to control IOP adequately. One patient complained of severe headache coincidental with increasing the strength of her medication; when the code was broken and it was revealed that she was in the timolol group, she was

TABLE 3

ADVERSE EXPERIENCES DURING STUDY

	Timolol Group (%)	Pilocarpine Group (%)
Mild stinging, burning, or smarting sensation briefly after instillation of drops (% of patients receiving medication who report symptom)		
Timolol 1/4% or pilocarpine 2%	2 (15)	2 (13)
Timolol 1/2% or pilocarpine 3%	2 (20)	2 (22)
Timolol 1% or pilocarpine 4%	5 (50)	2 (25)
Headache or brow ache		
Apparently related to drops	0	1
Apparently incidental to drops	2	1
Altered visual acuity with test drug or subjective sensation of darkened vision		
Mild	1*	3
Moderate	0	2
Severe	0	2

*Patient reported blurred vision at near but not distance. Examination revealed presbyopia appropriate for age which had been compensated by induced accommodation and miosis of prestudy glaucoma medication.

rechallenged (at her own request) with timolol 1% without recurrence of her headache. Another patient developed a papilloma of the right lower eyelid during the course of the study and the code was broken as a precautionary measure; he was in the pilocarpine group.

We compared the characteristics of patients who achieved adequate control of IOP to those whose pressures failed to be controlled (Table 4). Pilocarpine group patients who failed to reach adequately controlled IOPs were all receiving anticholinesterases and carbonic anhydrase inhibitors before entering the study. The two timolol group failures were receiving anticholinesterases. However, one patient whose prestudy medications were pilocarpine 4% and epinephrine 1% four times daily, echothiophate iodide 1/4% twice daily, and acetazolamide 250 mg four times daily, achieved adequate pressure control on timolol 1% alone. The patient was of South American origin, was darkly pigmented, and had dark brown irides. Baseline applanation pressure was the same for patients adequately or inadequately controlled in the timolol group; but for the pilocarpine group, baseline pressures were significantly higher in patients who subsequently failed, compared to those who were controlled ($P<.001$). Mean baseline facility of outflow was also significantly higher in patients who went on to control on pilocarpine compared to those who failed ($P<.005$).

Dose-response data are presented (Fig. 5). The timolol dose response is flat and does not suggest added benefit of the higher concentration in decreasing IOP; 0.25% and certainly 0.50% provided pressure reductions equal to 1.0%. There was a trend for higher pilocarpine concentrations to provide larger reductions in IOP, but the trend did not reach statistical significance. No statistically significant change occurred in pulse between the weakest and the strongest concentrations of timolol. Mean pulse rate in the pilocar-

TABLE 4

PRETREATMENT PATIENT CHARACTERISTICS

	Timolol Group*		Pilocarpine†	
	Adequate Control (No. = 10)	Inadequate Control (No. = 2)	Adequate Control (No. = 8)	Inadequate Control (No. = 4)
Prestudy medication‡				
P or E alone	7	0	4	0
P and E	2	0	3	0
CAI or EI, or both	1	2	1	4
Sex ratio (male:female)	6:4	0:2	4:4	3:1
Black/white/other	0/9/1	2/0/0	2/6/0	2/2/0
Dark/light/blue iris	2/2/6	2/0/0	4/2/2	3/1/0
Mean baseline app	34	34	28	43
Mean final app	21	28	21	39
Mean percent change§	52	25	37	12
Mean baseline pulse rate	79	79	81	74
Mean final pulse rate	68	69	84	89
Mean baseline C_{55}	.12	.16	.20	.07

*One patient withdrew; see text.

†Three patients withdrew; see text.

‡P designates pilocarpine; E, epinephrine; CAI, carbonic anhydrase inhibitor; EI, echothiophate iodide; app, applanation pressure in mm Hg; C_{55} facility of outflow using 1955 calibration.

§Mean percent change toward an assumed episcleral venous pressure of 10 mm Hg.

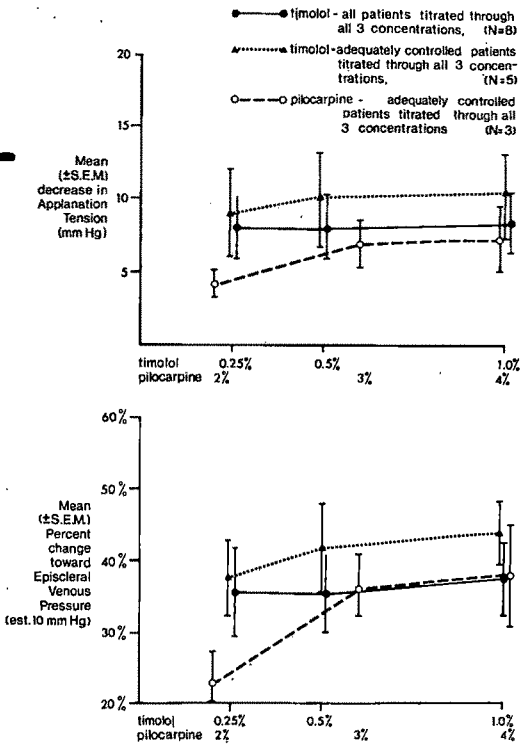


Fig. 5 (Boger and associates). Dose response for patients titrated over three or more weeks through all three concentrations of medication. All pilocarpine patients receiving all three concentrations also were adequately controlled and completed the ten-week maintenance period. Top, Results expressed as absolute decrease in applanation pressure. Bottom, Results expressed as percent change toward episcleral venous pressure, assumed to be 10 mm Hg.

pine treatment group did not differ significantly from baseline measurements at any of the concentrations used.

Discussion

Although there have been numerous reports of beta-adrenergic blocking agents decreasing IOP, most of these studies have involved single doses or short durations of therapy. For both propranolol[23,24] and atenolol[25] there is evidence that the short-term improvement in IOP dissipates in some patients after multiple dosing over prolonged periods. In this study using timolol ophthalmic solution, some patients exhibited an "escape" phenomenon over the first few days of therapy, but a significant decrease in IOP was still present two weeks into the maintenance period and remained undiminished after ten weeks of maintenance therapy. The two weeks of maintenance are referenced to the last titration visit and not to the baseline visit, so the patients had received timolol continuously for three weeks or more by the time they had their "two-week" visit. For a new medication to play an important role in open-angle glaucoma therapy, its action must be maintained over months and even years of continuous therapy. Timolol compares favorably to pilocarpine over a ten-week period. Figure 1, right, demonstrates a reduction in IOP after ten weeks of therapy similar to the 50% reduction reported by Zimmerman and Kaufman[20] in a single-dose study.

Timolol ophthalmic solution was uniformly well tolerated by the patients. An increased incidence of mild stinging was noted with the highest concentration of timolol, but none of the patients were troubled by it. The dose response data from this study (Fig. 3), and the single-dose study of Zimmerman and Kaufman,[21] indicates no added therapeutic advantage of 1% timolol over 0.5%. There is apparently no reason to study 1% solutions in further trials. A significant slowing of the pulse, the only important side effect noted in this study, appears to be a direct result of systemic absorption of this beta-adrenergic blocking agent. The blood pressure was not affected. Since mild systemic effects were clearly evident, the data have been analyzed per patient, rather than per eye. In their single-dose study, Zimmerman and Kaufman[20] recorded a decrease in the IOP of the untreated fellow eye in patients receiving timolol in one eye only. Although they wondered about systemic absorp-

tion, they apparently did not observe an alteration in pulse rate during the seven hours after instillation of the eyedrop. Katz and associates[19] also noted no alteration of pulse rate taken one hour after a single dose of timolol ophthalmic solution.

Timolol did not affect the pupil size and did not induce a spasm of accommodation. Many of the patients were pleased by the absence of the miotic effects. Routine observation of the fundus was also facilitated when the pupil was not miotic. It could be argued that the miosis of pilocarpine partly unmasked the design of the study. It was not completely unmasked, however. Although there was a clear differentiation in the means of pupil size, the interpretation of pupillary changes from visit to visit in an individual patient was not always so obvious. Some patients receiving miotics on a long-term basis continued to have small pupils through the baseline period even without glaucoma medication. Particularly with weaker solutions of pilocarpine the effects of the miosis and induced myopia were not necessarily evident to the examiner. The patients were also subject to uncertainty since they had had no previous experience with timolol. The paired information in this study was obtained as objectively as was practical in a situation where one medication had an undesirable side effect and the other did not.

The mean facility of outflow was significantly greater for adequately controlled patients receiving pilocarpine than for the timolol group. The population that responded adequately to timolol had a mean facility of outflow identical to the populations entering the study. Pilocarpine, on the other hand, adequately controlled only those patients with relatively good facilities of outflow. Although the group that received pilocarpine had a somewhat higher proportion of patients receiving maximal or near-maximal medication and with visual field abnormalities, the mean baseline facility of outflow (0.14) was similar to the mean facility (0.13) of the group that received timolol.

Tonography was done on all patients, but the results are not conclusive in establishing the mechanism of action of timolol. There was a trend for mean facility of outflow to increase while taking pilocarpine and timolol, but because of variability in the tonography data, these trends did not reach statistical significance. The mechanism by which timolol and other beta-adrenergic blocking agents decrease the IOP remains to be clearly established. The speculation by Elliott and associates[27] that $beta_1$ and $beta_2$ effects on aqueous human dynamics are opposite is difficult to reconcile with the fact that timolol is at least as effective as the β_1 adrenergic blocking agent, atenolol.[25,27,28–30]

SUMMARY

A ten-week, double-masked, randomized, clinical trial compared timolol ophthalmic solution and pilocarpine in the therapy of open-angle glaucoma. Timolol decreased the intraocular pressure at least as much as pilocarpine and did not induce miosis, accommodative spasm, or other annoying side effects. The pulse was slowed by timolol, but blood pressure was unaffected. Significant decreases in intraocular pressure were still present after ten weeks of maintenance therapy with the same concentration of drug.

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MACKAY-MARG TONOMETRY OVER THERAPEUTIC SOFT CONTACT LENSES

ROGER F. MEYER, M.D., RALPH M. STANIFER, M.D., AND KATHRYN C. BOBB, B.A.

Ann Arbor, Michigan

The need to record postoperative intraocular pressure (IOP) in penetrating keratoplasty patients has been stressed over recent years.[1,2] Aphakic penetrating keratoplasty patients often have a marked rise in early postoperative IOP.[3,4] A clinically reliable method for following IOP in patients after keratoplasty is by Mackay-Marg electronic applanation tonometry.[5–7] Generally, Mackay-Marg tonometry directly over a recent corneal graft poses no problem. However, occasionally, the graft epithelium fails to heal after surgery, or recurrent epithelial defects develop which fail to heal by pressure patching. In such patients, therapy with bandage contact lenses is beneficial.[8–12] For the therapeutic contact lens to achieve its effect, it must remain in position over the graft continually until epithelial healing is complete.[12] During this time, when the graft is covered with a therapeutic soft contact lens, accurate IOP measurement poses a problem. If the contact lens is removed, epithelial wound healing may be hindered. If IOP is not monitored for a prolonged period of time, glaucomatous damage to the eye may occur. The concurrent need to check IOP postoperatively without disturbing the graft epithelium by contact lens removal prompted us to evaluate the accuracy of Mackay-Marg tonometry through therapeutic soft contact lenses.

From the Department of Ophthalmology, University of Michigan Medical School, Ann Arbor, Michigan. This study was supported in part by the Michigan Eye Bank.

Reprint requests to Roger F. Meyer, M.D., Department of Ophthalmology, University of Michigan Medical School, Ann Arbor, MI 48109.

MATERIAL AND METHODS

Experiment 1. *Mackay-Marg tonometry over therapeutic soft contact lenses on eye bank eyes*—Twelve eye bank eyes stored in moist chambers were cannulated through the optic nerve with a 16-gauge needle to manometrically control IOP, as described by Hilton and Schaffer.[13] The eyes were mounted on a wooden block and held in position by a metal frame and cotton gauze. A mercury manometer was used to control and vary the IOP of the eyes throughout a range of 10 through 50 mm Hg. The Mackay-Marg tonometer (model #255) was used for measurement of IOP. Bausch and Lomb Plano-T therapeutic soft contact lenses were used as the bandage lenses. Intraocular pressure was measured first without the therapeutic soft contact lens and then with the lens in place. Eight applications of the applanating probe were made in each instance; the lowest consistent series of readings was accepted as the most valid estimate of IOP in accordance with the manufacturer's recommendations. The investigator reading the tracings had no prior knowledge of the manometric pressure or whether the tracings were taken with or without the therapeutic lens in place.

Experiment 2. *Mackay-Marg tonometry over therapeutic soft contact lenses in postoperative keratoplasty patients*—Over the past two years, 18 patients were treated with therapeutic soft contact lenses for epithelial healing problems after penetrating or lamellar keratoplasty. Of these, 13 patients had penetrating keratoplasty and five patients had lamellar keratoplasty. Twenty-one volunteers with

normal corneas and normal IOPs served as controls. Intraocular pressure was always measured by the same observer using the same instrument, first without the therapeutic soft contact lens and then with the lens in place. All tracings were made with the eyes anesthetized with topical proparacaine and the patient in a sitting position. A disposable rubber film was used on the probe tip to protect it and the patient's eye during the measurements. The probe, which has a 1.5-mm applanating surface and does not require fluorescein, was placed against the central graft or over the therapeutic contact lens over the corneal graft. In the controls, the readings were taken over the central cornea and repeated with the therapeutic contact lens over the cornea. Only the results in patients on whom measurements could be obtained both without and with the therapeutic lens in place were included in the study.

TABLE 1

DIFFERENCES IN IOP READINGS WITHOUT AND WITH THERAPEUTIC SOFT CONTACT LENSES ON EYE BANK EYES

	Manometrically Controlled IOP* (mm Hg)			
Eye	11-20	21-30	31-40	41-50
1	—	0	−2	0
2	—	+2	+1	+4
3	0	0	+1	+4
4	+1	0	+2	−3
5	−1	+4	0	0
6	+2	+4	+1	0
7	+2	+2	+3	−1
8	+2	0	—	−2
9	−5	−1	0	+2
10	0	—	0	−1
11	0	+2	+3	—
12	+2	−3	0	—

*—Indicates no tracings were obtained within specified range; 0, no difference in IOP readings; negative number, IOP with lens was lower than without lens; positive number, IOP with lens was higher than without lens.

RESULTS

Experiment 1. *Mackay-Marg tonometry over therapeutic soft contact lenses on eye bank eyes*—Comparisons of pressure readings without and with the therapeutic lens in place were made at increments of 10 mm Hg. Only readings between 10 and 50 mm Hg were used. The difference in pressure readings without and with the lens in place ranged from −5.0 to +4.0 mm Hg (Table 1). The mean difference between readings with and without the therapeutic soft contact lens in place was +0.6 mm Hg; this indicates that the reading averaged 0.6 mm Hg higher when taken over the contact lens. A *t*-test showed the mean difference was not statistically significant ($P<.05$).

In a comparison of the four pressure groupings, no statistically significant difference in the reliability of the readings was noted over a range of 10 through 50 mm.Hg IOP ($P>.50$).

A 95% confidence interval on future observations was constructed from this data and found to range from −4.7 to +3.6 mm Hg. This indicates that the difference in intraocular pressure as recorded without and with the therapeutic soft contact lens in place on eye bank eyes will range between −4.7 and +3.6 mm Hg 95% of the time.

Experiment 2. *Mackay-Marg tonometry over therapeutic soft contact lenses in postoperative keratoplasty patients*—Readable tracings were obtained without and with the therapeutic soft contact lens in position when the probe tip was carefully placed. Often the tracings with the therapeutic lens in place were more easily readable than tracings over the same graft without the therapeutic lens. We compared the IOP readings without and with the therapeutic soft contact lens in place in postoperative penetrating keratoplasty patients and found that the difference ranged from −3.0 to +6.0 mm Hg (Table 2). The mean difference was 1.5 mm Hg

TABLE 2

DIFFERENCES IN IOP READINGS WITHOUT AND WITH THERAPEUTIC SOFT CONTACT LENS AFTER PENETRATING KERATOPLASTY*

	IOP (mm Hg)		
Patient No.	Without SCL	With SCL	Difference*
1	14	14	0
2	29	35	+6
3	40	42	+2
4	41	42	+1
5	24	38	+4
6	36	40	+4
7	31	32	+1
8	12	12	0
9	28	32	+4
10	23	30	−3
11	17	17	0
12	34	32	−2
13	19	22	+3

*SCL designates soft contact lens.

higher with the lens in place. A *t*-test showed the mean difference was not statistically significant ($P<.05$).

In postoperative lamellar keratoplasty patients, a comparison of IOP readings without and with the lens revealed a range of difference from 0 to +3.0 mm Hg (Table 3). The mean difference was 0.6 mm Hg higher with the lens in place. A *t*-test showed the mean difference was not statistically significant ($P<.05$).

In normal volunteers, the difference in IOP readings without and with the lens in place ranged from −3.0 to +2.0 mm Hg (Table 4). The mean difference was 0.3 mm Hg lower with the lens in place. A *t*-test showed the mean difference was not statistically significant ($P<.05$).

Confidence intervals were constructed by using the above data to predict the reliability of future observations (Table 5). Results revealed that with 95% confidence the difference between IOP read-

TABLE 3

DIFFERENCES IN IOP READINGS WITHOUT AND WITH THERAPEUTIC SOFT CONTACT LENS AFTER LAMELLAR KERTOPLASTY*

	IOP (mm Hg)		
Patient No.	Without SCL	With SCL	Difference
1	20	20	0
2	15	15	0
3	24	24	0
4	22	25	+3
5	43	43	0

*SCL designates soft contact lens.

TABLE 4

DIFFERENCES IN IOP READINGS WITHOUT AND WITH THERAPEUTIC SOFT CONTACT LENS IN NORMAL EYES*

	IOP (mm Hg)		
Patient No.	Without SCL	With SCL	Difference
1	18	16	−2
2	20	21	+1
3	21	22	+1
4	24	21	−3
5	21	23	+2
6	16	17	+1
7	17	17	0
8	21	23	+2
9	26	24	−2
10	18	19	+1
11	22	22	0
12	17	17	0
13	22	20	−2
14	20	21	+1
15	19	19	0
16	21	19	−2
17	22	21	−1
18	18	17	−1
19	19	18	−1
20	18	18	0
21	18	17	−1

*SCL designates soft contact lens.

TABLE 5

PREDICTED RANGE OF VARIATION BETWEEN IOP MEASUREMENTS WITHOUT AND WITH THERAPEUTIC LENS WITH 95% CONFIDENCE ON FUTURE OBSERVATIONS.

	Predicted Range
Eye bank eyes	−4.7 to +3.6 mm Hg
Penetrating keratoplasties	−4.3 to +7.4 mm Hg
Lamellar keratoplasties	−3.5 to +4.7 mm Hg
Normal eyes	−3.3 to +2.7 mm Hg

ings without and with a therapeutic lens in place may range from −4.3 to +7.4 mm Hg in postoperative penetrating keratoplasty patients. In postoperative lamellar graft patients, the difference may range from −3.5 to +4.7 mm Hg, and in normal eyes from −3.3 to +2.7 mm Hg.

Discussion

It is important to know the IOP in a patient who is wearing a therapeutic soft contact lens. Also, it is important to know whether it is accurate to measure the IOP through the lens using the Mackay-Marg tonometer. This situation frequently arises after penetrating keratoplasty, especially in the aphakic patient, where there is considerable risk of secondary glaucoma which might otherwise go undiagnosed and untreated.[3,4,14,15] Measurement of IOP after keratoplasty by Goldmann applanation or Schiøtz tonometry is not reliable.[7,16] The Mackay-Marg electronic applanation tonometer, however, is useful in normal eyes[17–19] and in eyes after keratoplasty.[5–7] Although the pneumatic applanation tonometer may be useful in keratoplasty patients, the Mackay-Marg tonometer remains the instrument of choice.[20] It was used in our studies because of its accuracy, maneuverability, and reproducibility.

Previous studies of tonometry over soft contact lenses on normal corneas reported good correlation between readings taken without and with the lens in place when using Schiøtz or Mackay-Marg tonometers.[21] Reproducible readings could not be obtained over soft contact lenses with the Goldmann applanation tonometer because of an inadequate mire pattern quality. In another study, using a pneumatic applanation tonometer over soft contact lenses in normal and diseased corneas, it was found that satisfactory IOP readings were recorded both without and with the soft lenses.[22] The readings with the lenses in place were believed to reflect accurate and reliable pressure readings. Inaccurately high values did occur, however, when the thickness of the soft lens exceeded 0.45 mm centrally. Also, inaccurate readings were obtained when the lens had been worn continuously for longer than three months in certain disease states; this was considered to be caused by the lipid and protein build-up causing a change in the elasticity of the lens.

In this preliminary study we found that readable tracings could be obtained in eye bank eyes, postoperative keratoplasty patients, and normal eyes with a therapeutic soft contact lens in place. However, the reliability of the readings was variable. Our total number of patients was small and we were limited by the number of IOP readings. Readings taken over the therapeutic lenses were not in absolute agreement with the readings taken without the lenses. Although the mean differences between the readings within the respective groups of patients were small, when the variances were used statistically to construct confidence intervals on any one future observation, the range of difference greatly increased. The difference might be acceptable as an estimate of IOP not requiring precisely accurate numbers. Such readings are probably adequate as a guide to the necessity of treating increased IOP in postoperative keratoplasty patients, and they are more accurate than the tactile tension method. However, it is not reliable enough to establish a diagnosis of chronic glaucoma, a situation in which the accurate measurement of IOP is crucial because of the damaging effects of chronic pressure increase. If an accurate IOP measurement is necessary, the soft contact lens should be removed and IOP recorded directly over the corneal graft even though a small hindrance to epithelial wound healing may result.

SUMMARY

We evaluated the accuracy of Mackay-Marg electronic applanation tonometry over Bausch and Lomb Plano-T therapeutic soft contact lenses on eye bank, postoperative keratoplasty, and normal eyes. Intraocular pressure (IOP) measurements were compared in the same eye without and with the lens in place. The mean difference of IOP readings through the lens was not statistically different from that without the lens over an IOP range of 10 through 50 mm Hg. We constructed confidence intervals to predict the accuracy of future observations. Results revealed that with 95% confidence, the range of difference between IOP readings without and with the lens in place was from −4.7 to +3.6 mm Hg in eye bank eyes, from −4.3 to +7.4 mm Hg in postoperative penetrating keratoplasty patients, from −3.5 to +7.4 mm Hg in postoperative lamellar keratoplasty patients, and from −3.3 to +2.7 mm Hg in normal eyes. We concluded that IOP can be measured with the Mackay-Marg tonometer through a therapeutic soft contact lens over a corneal graft. Although the readings are not as accurate as without the lens, they are probably adequate as a guide to the necessity of treating increased IOP in postoperative keratoplasty patients.

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CYCLOCRYOTHERAPY IN NEOVASCULAR GLAUCOMA

THEODORE KRUPIN, M.D., KENNETH B. MITCHELL, M.D.,
AND
BERNARD BECKER, M.D.
St. Louis, Missouri

The treatment of eyes with rubeosis iridis and neovascular glaucoma is often less than satisfactory. Topical cycloplegics and corticosteroids may relieve pain, but do not control the glaucoma.[1] Carbonic anhydrase inhibitors may decrease intraocular pressure, but rarely provide satisfactory control. Conventional filtration surgery is rarely successful. Cyclocryotherapy is considered by some to be the preferred treatment.[2-4] However, most studies on this mode of treatment include relatively few patients and short-term follow-up. We report herein a large series of patients with long-term follow-up after cyclocryotherapy for neovascular glaucoma.

MATERIAL AND METHODS

Between January 1972 and January 1976, 50 patients with neovascular glaucoma were treated with cyclocryotherapy for uncontrolled intraocular pressure and associated pain. Adequate clinical information and postoperative follow-up were obtained for 46 patients (50 eyes). Thirty patients were men; 41 were white. The age at surgery was 60.6 ± 11.8 years (mean ± S. D.). Bilateral cyclocryotherapy was performed on four patients. Four eyes required a repeat procedure.

Rubeosis iridis was associated with unilateral retinal vascular occlusion in 21 eyes. Five of these patients had diabetes mellitus, three had primary open-angle glaucoma, and four had chronic angle-closure glaucoma. Neovascular glaucoma occurred in 28 eyes of 24 patients with proliferative diabetic retinopathy, four of whom were juvenile diabetics. One patient had neovascular glaucoma in association with a retinal angioma with exudative retinal detachment.

Cyclocryotherapy was performed under retrobulbar anesthesia. A retinal cryoprobe (2.5 mm diameter) was centered approximately 2 to 3 mm posterior to the corneoscleral limbus over the entire circumference of the ciliary body. Two eyes had eight applications, whereas the remainder had 12. A single freeze-thaw technique (45 to 60 seconds) was performed on 25 eyes at −60° C and on 15 eyes at −80° C. A freeze-thaw-refreeze technique (20 to 30 seconds per freeze) at −80° C was performed on 14 eyes. All eyes received topical cycloplegics and corticosteroids postoperatively.

RESULTS

The mean postoperative follow-up was 24.9 ± 13.9 months. Forty-five eyes were observed for 12 months or longer. Of the five eyes observed for less than 12 months, three were enucleated for persistent pain, and two patients died.

Mean preoperative intraocular pressure was 51.8 ± 14.0 mm Hg. Many eyes showed an initial increase in pressure several hours after the procedure, which lasted for varying periods of time. During the first 12 months following cyclocryotherapy, 14 eyes (28%) had intraocular pressures greater than 26 mm Hg, 29 (58%) had 25 mm Hg or less (11 of these

From the Department of Ophthalmology and the Oscar Johnson Institute, Washington University School of Medicine, St. Louis, Missouri. This study was supported in part by research grant EY 00336 and a Research Career Development Award EY 00082 (Dr. Krupin) from the National Eye Institute, Bethesda, Maryland. Dr. Mitchell was a Heed Foundation Fellow (1977-1978).

Reprint requests to Theodore Krupin, M.D., Department of Ophthalmology, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110.

less than 10 mm Hg), and seven (14%) became phthisical. The intraocular pressures in two of the three eyes enucleated were over 40 mm Hg, and the third eye was phthisic. One patient who died within the first year had pressures greater than 40 mm Hg, whereas the other had pressures less than 10 mm Hg. Intraocular pressure at the last examination was greater than 26 mm Hg in 16 (32%) eyes and 25 mm Hg or less in 17 (34%) eyes, and 17 (34%) eyes were phthisic. Phthisis developed at a mean of 14.4 ± 9.6 months after cyclocryotherapy. The final intraocular pressure in the four eyes undergoing repeat treatment was greater than 26 mm Hg in three eyes and less than 25 mm Hg in one eye.

Nine eyes (18%) had no light perception before cyclocryotherapy (Table 1). Twenty-four of the remaining eyes (58.5%) lost light perception at an average of 11.2 ± 10 months following treatment. In these eyes, preoperative vision was 6/120 (20/400) or better in three eyes, finger counting in six eyes, hand motion in eight eyes, and light perception in seven eyes. A dense cataract developed after the procedure in ten eyes. Anterior segment necrosis developed in four eyes in the immediate postoperative period. Three of these eyes have been studied previously.[5] All patients were comfortable except for the three that required enucleation.

The final intraocular pressure, visual acuity, and the development of phthisis bulbi were related neither to the number of cryogenic lesions nor to the manner of their application.

TABLE 1
VISUAL ACUITY OF 50 EYES BEFORE AND AFTER CYCLOCRYOTHERAPY

Visual Acuity	No. of Eyes	
	Preoperative	Postoperative*
6/12-6/30 (20/40-20/100)	3	2
6/60-6/120 (20/200-20/400)	4	0
Finger counting	9	0
Hand motion	16	6
Light perception	9	9
No light perception	9	33

*Mean 24.9 ± 13.9 months.

DISCUSSION

Rubeosis iridis apparently results from chronic ocular ischemia.[6,7] Iris neovascularization usually begins at the pupillary margin with subsequent growth of fibrovascular tissue in the peripheral iris and trabecular meshwork.[8] Angle vessel[9] or panretinal photocoagulation[10] appears to be beneficial before fibrovascular tissue has significantly closed the angle. Once neovascular glaucoma is established, these therapies are usually ineffective. Results of routine filtration procedures are disappointing. Either prolonged postoperative inflammation or continued growth of fibrovascular tissue may close the filtration site.

Cyclocryotherapy may decrease ciliary body blood flow and obliterate the capillary circulation of the ciliary processes.[11–13] Decrease in aqueous production and intraocular pressure with relief of pain and maintenance of vision are the goals of therapy. The variability of the response to treatment may be influenced by the number, size, location, temperature, duration, and extent of the cryogenic lesions. Individual variations in uveal blood flow may play a major role. Cryotherapy may intensify ocular ischemia and produce complications of acute anterior segment necrosis and late phthisis bulbi. According to a personal communication from A. R. Rosenthal, M.D., anterior segment ischemia may follow cryotherapy to only one half of the circumference of the ciliary body.

The results of cyclocryotherapy for neovascular glaucoma in our study were less favorable than previous reports (Table 2). Our series was followed for a longer period after treatment. Most patients (47 of 50 eyes) achieved ocular comfort. However, the number of eyes

TABLE 2
EFFECTS OF CYCLOCRYOTHERAPY IN NEOVASCULAR GLAUCOMA

	Feibel-Bigger[2]	Boniuk[4]	Bellows and Grant[3]	Present Study
Eyes	38	19	10	50
> 1 year follow-up	8	11		45
Final intraocular pressure control	24 (63%)		3 (30%)	17 (34%)
Hypotony (< 10 mm Hg)	12 (32%)	7 (37%)		5 (10%)
Phthisis bulbi		2 (10%)	1 (10%)	17 (34%)
Loss of light perception	14/35 (40%)	8/17 (47%)		24/41 (58.5%)
Enucleation	3 (8%)	4 (21%)		3 (6%)

demonstrating pressure control decreased (to 36%), and the development of phthisis bulbi (34%) and the loss of light perception (58.5%) increased with the length of postoperative follow-up.

Because of the high incidence of serious complications, we believe there is a need for other forms of therapy for eyes with vision potential. Bipolar cautery to the ciliary processes in combination with trabeculectomy (according to unpublished data of J. Herschler, M.D.), a seton to maintain patency of the sclerostomy site,[14] or a modified glaucoma valve implant[15] are all feasible alternatives.

SUMMARY

To determine the long-term effects of cyclocryotherapy, we conducted a follow-up with a mean of 24.9 ± 13.9 months in 50 eyes of 46 patients with neovascular glaucoma. On final examination, intraocular pressure in 16 (32%) of the eyes was > 26 mm Hg and in 17 (34%), ≤ 25 mm Hg; 17 (34%) developed phthisis bulbi. Enucleation was performed in three of the eyes. Anterior segment necrosis occurred immediately postoperatively in four eyes. Twenty-four of 41 eyes (58.5%) with vision lost light perception during our study. All patients were comfortable except the three who required enucleation.

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RETINAL SURGERY COMPLICATED BY A SPONTANEOUSLY ACQUIRED FACTOR VIII INHIBITOR

IRA A. PRILUCK, M.D., ROBERT B. HOWE, M.D., DAVID E. EIFRIG, M.D., J. ROGER EDSON, M.D., AND KENNETH MILLER, M.D.

Minneapolis, Minnesota

Inherited deficiencies of blood clotting factors VIII, IX, and XIII have resulted in hemorrhagic complications in ophthalmic surgery.[1–3] Our study reports a case of an acquired factor VIII deficiency due to a spontaneously occurring blood factor inhibitor in a previously healthy individual. This coagulopathy first manifested itself as a delayed hemorrhagic choroidal detachment. The hemorrhagic disorder was treated effectively by the combined use of high dose factor VIII and immunosuppressive therapy. We review herein the role of this therapeutic regimen in patients with acquired factor VIII antibodies. Using readily available coagulation laboratory studies, we outline an approach to detect inherited or acquired hemostatic problems.

CASE REPORT

The patient was a 77-year-old man who had undergone an unsuccessful retinal reattachment procedure in his right eye in 1954. Three days before admission to the hospital, he noted a sudden decrease in vision and a "veil" in his left eye. Initial eye examination revealed the vision to be light perception with poor projection in the right eye and 6/120 (20/400) in the left eye. Slit-lamp biomicroscopy revealed a quiet anterior segment bilaterally. Intraocular pressure was R.E.: 16 mm Hg; L.E.: 20 mm Hg. Forty-five diopters of right exotropia was present. Opthalmoscopic examination of the left eye revealed an aphakic rhegmatogenous retinal detachment. The patient had undergone major surgery previously without incident, the family history was noncontributory for bleeding disorders, and he was not taking any systemic medication.

From the Departments of Ophthalmology (Drs. Priluck and Eifrig); Laboratory, Medicine and Pathology (Drs. Edson and Miller); Hematology (Dr. Howe); and Pediatrics (Dr. Miller), the University of Minnesota, Minneapolis, Minnesota. This study was supported in part by National Eye Institute Research Grant EY00027.

Reprint requests to Ira A. Priluck, M.D., Department of Ophthalmology, Mayo Clinic, Rochester, MN 55901.

The patient had an uneventful buckling procedure with release of subretinal fluid on the second day in the hospital. The next day his retina appeared flat, and there were no postoperative complications. However, on the fourth postoperative day he had a large hemorrhagic choroidal detachment (Fig. 1) and an orbital hematoma. He subsequently developed gastrointestinal bleeding, and his hemoglobin decreased from a preoperative value of 14.3 to 8.5 g/100 ml. The platelet count was 346,000. A coagulation screening battery revealed a prothrombin time of 11.5 seconds (normal, 10 to 13 seconds), a partial thromboplastin time of 60.3 seconds (normal, 35 to 45 seconds), and a thrombin time of 16.4 seconds (normal, 15 seconds). The factor VIII level was 18%, and an inhibitor to factor VIII was demonstrable by in vitro assay.

The patient was then transferred to the Medical Service and received the following drugs: prednisone 100 mg daily in four divided doses, and cyclophosphamide 300 mg/m^2 initially (intravenously), followed by 10 mg/kg of body weight postoperatively daily for three days. Factor VIII concentrate was given as thromboplastinogen (cryoprecipitate) 30 donor units initially, followed by four units every two hours for the first 24 hours and gradually reduced as the factor VIII level rose from an initial level of 18% to 75% at the time of discharge (Fig. 2). Hemostasis was achieved within 36 hours following

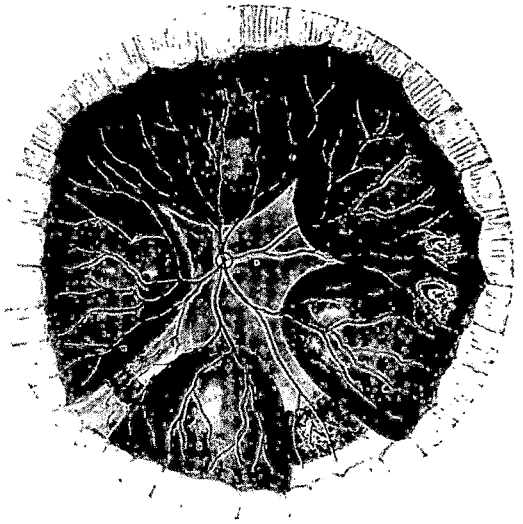


Fig. 1 (Priluck and associates). Schematic representation of hemorrhagic choroidal detachment following scleral buckle.

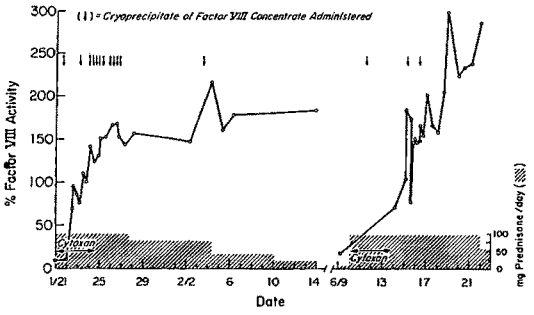


Fig. 2 (Priluck and associates). Diagrammatic representation summarizing therapy during two hospitalizations.

the institution of this therapeutic regimen. The prednisone was gradually reduced over the next six months to 10 mg daily. During this time interval, the patient's hemorrhagic choroidal detachment slowly resolved; however, his retina redetached. He was subsequently readmitted for a second scleral buckling operation. Preoperatively, he was treated with immunosuppressive therapy consisting of prednisone 100 mg daily and cyclophosphamide 600 mg for three days. He received an additional 2,000 units of factor VIII concentrate preoperatively and 2,000 units 24 hours later which maintained his factor VIII level above 100%. He tolerated the drugs without untoward bleeding, and the retina remained flat postoperatively. Re-examination six months later revealed the vision to be 6/120 (20/400) in the left eye. He now receives 20 mg of prednisone daily.

DISCUSSION

Acquired clotting factor inhibitors have been reported against factors V, VIII, IX, X, XI, and XIII, and von Willebrand's factor.[4,5] The majority of the inhibitors have been factor VIII antibodies. In the hemophiliac, factor VIII antibodies develop as a complication of replacement therapy.[4,6–8] Blood clotting inhibitors also occur in certain systemic states including autoimmune disorders, drug hypersensitivities, postpartum, paraproteinemias, and they have been reported to occur spontaneously in otherwise healthy individuals.[9]

The factor VIII inhibitors are primarily gamma globulins of the IgG_3 or IgG_4 subclass which contain exclusively (or predominantly) one light chain, namely, either λ or κ.[4–5,10–12] Occasionally, an IgM or IgA inhibitor has been reported.[13,14] They are specifically directed against factor VIII as demonstrated by incubation studies in which factor VIII activity diminishes when the antibody is added.[10–12,15] These antibodies do, however, differ from classical antibodies in that they do not precipitate with the antigen and are not complement-fixing.[4,5]

The development of an inhibitor in a previously healthy individual may result in serious and often life-threatening hemorrhage. In the majority of instances, the patient is asymptomatic unless hemostatically challenged. Therefore, one cannot rely solely on a noncontributory bleeding history to exclude the presence of an inhibitor. Only a coagulation screening battery consisting of a prothrombin time, partial thromboplastin time, and thrombin time will detect an acquired hemostatic abnormality. A simplified version of the human plasma coagulation system appears in Figure 3. The partial thromboplastin time detects inherited defects in the intrinsic clotting system such as hemophilia A (factor VIII deficiency), and hemophilia B (factor IX deficiency).

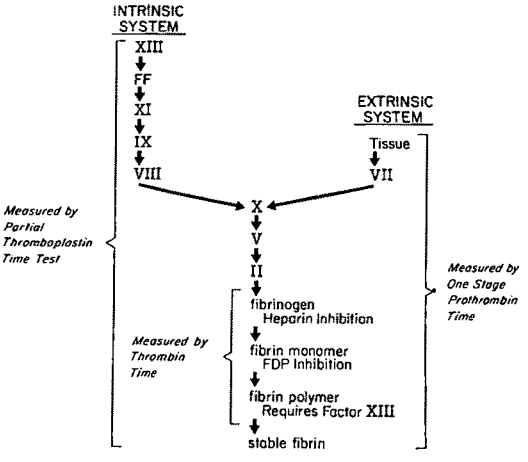


Fig. 3 (Priluck and associates). Simplified coagulation scheme showing routine coagulation studies related to the clotting factors. (Roman numerals follow standard nomenclature; FDP, fibrin degradation produce; FF, Fletcher factor).

The prothrombin time detects abnormalities in the extrinsic pathways, such as factor VII deficiency, and is often useful to detect vitamin K deficiency or clotting abnormalities associated with liver disease. This test is perhaps best used for the monitoring of oral anticoagulant therapy (Coumadin, Warfarin). The thrombin time is a useful test to monitor heparin therapy. When prolonged, it may also be indicative of elevated fibrin or fibrinogen degradation products, abnormal fibrinogens, a low fibrinogen, or the presence of abnormal macromolecules such as myeloma protein.[16] These three tests (prothrombin time, partial thromboplastin time, thrombin time) combined with a platelet count and a template bleeding time (the latter two studies to evaluate platelet function and vascular integrity) form a comprehensive screening battery in any preoperative patient.

The course of acquired factor VIII inhibitors is variable.[4] Furthermore, because of the many causes of factor VIII antibodies, no one standardized therapeutic regimen has been used. Thus, few generalizations can be made in the treatment of these patients. Successful treatment programs have included the use of bovine or porcine factor VIII concentrates[17,18]; corticosteroids, with or without other cytotoxic agents[4,5,19–23]; exchange transfusion[24,25]; and prothrombin complex concentrates.[26,27] Although spontaneous disappearance of inhibitors may occur in the postpartum patient as well as in patients in whom it has occurred with drug usage, it is uncommon in the patient with the spontaneously acquired inhibitor. The majority of these patients have responded to high dose factor VIII concentrate combined with prednisone and a cytotoxic agent with exchange transfusion occasionally necessary for the acute life-threatening bleeding episode.[24,25] Prothrombin complexes, on the other hand, should be reserved for the patient in whom other forms of therapy have failed, because of the inherent risk of thrombogenesis and hepatitis.[26,27]

The duration of treatment for an acquired inhibitor once remission is achieved is still open to question.[5] Although sustained remissions generally occur after cessation of therapy, the inhibitor may reappear. Therefore, it is imperative that coagulation studies and specific factor assays be followed in the patient with a history of an idiopathic, acquired factor VIII inhibitor, especially if further surgery is contemplated.

SUMMARY

We studied a factor VIII inhibitor spontaneously occurring in an otherwise healthy patient who underwent retinal reattachment. The clotting defect first manifested itself as a delayed hemorrhagic choroidal detachment. His bleeding diathesis was successfully managed by infusion of factor VIII concentrate, prednisone, and cyclophosphamide. Surgical procedures in patients with severe bleeding disorders present a difficult therapeutic problem which can be effectively managed by the close cooperation of the surgeon, hematologist, coagulation laboratory, and blood bank.

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DILATED EPISCLERAL VESSELS AND OPEN-ANGLE GLAUCOMA

RONALD L. RADIUS, M.D., AND A. EDWARD MAUMENEE, M.D.
Baltimore, Maryland

The present report describes four patients with dilated, tortuous episcleral vessels. In three of these patients, open-angle glaucoma with characteristic disk and field pathology was associated with this vascular anomaly. Glaucoma with episcleral congestion has been described in patients with carotid-cavernous-sinus fistula and in other orbital obstructive lesions.[1–4] Unilateral glaucoma has also been documented in cases of orbital hemangiomatosis.[5–8] On the other hand, although familial cases of open-angle glaucoma with increased episcleral venous pressure have been cited,[9,10] association of idiopathic dilated episcleral vessels and open-angle glaucoma appears to be less well recognized.

CASE REPORTS

Case 1—This 63-year-old white woman was first seen in consultation in 1949. She had been referred to the Wilmer Institute for examination of unilateral glaucoma of the right eye. Visual acuity was 6/6 (20/20) bilaterally. The most striking aspects of her examination were the markedly tortuous dilated episcleral vessels present bilaterally, but much more prominent in the diseased right eye (Figs. 1 and 2). These vessels appeared to originate near the insertion of the rectus muscles; they then became confluent and encircled the corneoscleral limbus. By history, this vascular abnormality had been present since childhood. There was no family history of either similar vascular anomalies or glaucoma. General physical examination failed to demonstrate any systemic pathology that might account for the vascular abnormality.

Despite medical therapy, intraocular pressures (IOPs) in the right eye were consistently greater than 30 mm Hg. Goldmann perimetry demonstrated an early nasal step defect in the peripheral visual field. Intraocular pressures in the left eye were between 15 and 20 mm Hg, and the visual field was unremarkable. Gonioscopy in both eyes revealed normal grade-III open angles without any obvious vascular abnormalities.

Because of persistent increase in IOP and early visual field loss, penetrating cyclodiathermy was performed in the right eye. Treatment was repeated in 1954. Results of examination were essentially unchanged in 1958. Both eyes showed tortuous dilated episcleral vessels, although involvement in the glaucomatous right eye was more marked. The right eye continued to have IOP as high as 30 mm Hg, with nerve head pallor and glaucomatous cupping. As before, perimetry demonstrated a nasal step defect in the peripheral field; tonography revealed decreased facility of outflow, 0.06 μl/min/mm Hg. The left eye continued to have normal IOPs and visual field function, and facility of outflow was 0.18 μl/min/mm Hg. Repeat cyclodiathermy ultimately controlled pressure increase in the treated right eye.

By 1971, 23 years after her first ocular surgery, cataract had reduced vision in her right eye to hand motions. Intraocular pressure was controlled at 11 mm Hg. For the first time, however, pressure increase in the previously uninvolved left eye was documented, and was recorded as high as 26 mm Hg. Tonography showed reduced facility of outflow of 0.10 μl/min/mm Hg. Visual field examination showed a nasal step defect. The optic nerve head of the left eye showed increased cupping, with a cup: disk ratio of 0.9.

Gradual progression of bilateral cataracts necessitated lens extraction. Surgery on the right eye was performed through a clear corneal incision, but in the left eye, a corneoscleral limbus-based conjunctival flap and corneoscleral section were used. No untoward complications or excessive bleeding from prominent episcleral vessels occurred during either procedure.

The patient was last seen in February 1977, at which time aphakic correction afforded visual acuity of 6/6 (20/20) bilaterally. By means of topical pilocarpine, 2%, in the left eye only, IOPs remained below 20 mm Hg. Disk morphology and visual field function were unchanged.

Case 2—This 42-year-old man was first seen in 1969, with IOP increase in the right eye. Visual acuity was R.E.: 6/6 (20/20); L.E.: 6/4.5 (20/15). External examination revealed prominent, dilated episcleral vessels bilaterally. As in Case 1, this anomaly was more marked in the glaucomatous right eye (Figs. 3 and 4). By history, these vessels had been present for at least ten years. There was no family history of glaucoma or ocular vascular anomalies. Medical evaluation did not reveal any cause for these dilated vessels.

Intraocular pressures were 35 mm Hg in the right eye and 14 mm Hg in the left eye. Gonioscopy revealed open angles, grade III, bilaterally. In the right eye, despite pressure increase to 35 mm Hg,

From the Wilmer Ophthalmological Institute, Johns Hopkins Hospital, Baltimore, Maryland.

Reprint requests to A. Edward Maumenee, M.D., the Wilmer Institute, Johns Hopkins Hospital, 601 N. Broadway, Baltimore, MD 21205.

Schlemm's canal was engorged with blood. Tonography documented a reduced facility of outflow in the right eye of 0.12 μl/min/mm Hg, whereas that of the left eye was within normal limits at 0.25 μl/min/mm Hg. The right optic nerve head showed glaucomatous cupping; the left optic disk appeared normal. Goldmann perimetry revealed extensive visual field loss in the right eye inferiorly. Visual field function in the left eye was normal.

Because of persistent IOP increase and extensive peripheral visual field loss, the right eye underwent filtration surgery involving corneoscleral cautery under a corneoscleral limbus-based conjunctival flap. Postoperatively, IOPs remained below 20 mm Hg in the right eye.

The patient was seen most recently in April 1977; his visual acuity was still slightly reduced in the right eye. A flat, diffuse filtering bleb involving superior conjunctiva was present in the right eye, and the IOP was 15 mm Hg. For the first time, however, IOP as high as 26 mm Hg was noted in the left eye. Tonography at that time revealed a reduced facility of outflow of 0.16 μl/min/mm Hg in the left eye. Visual field examination remained unchanged, with extensive inferior field loss in the right eye, and normal visual field function in the left eye.

Case 3—This 48-year-old white woman was first seen in consultation in 1977. For the previous four years, she had been observed elsewhere for glaucoma of the right eye. Because of prominent episcleral vessels, medical examination, including cranial arteriography, has been done for possible carotid-cavernous-sinus disease, but no vascular abnormality was found. There was no family history of either glaucoma or ocular vascular anomalies.

Initial examination here revealed visual acuity of 6/6 (20/20) bilaterally. As in the previous two cases, there were dilated tortuous episcleral vessels of both eyes, but with more involvement in the glaucomatous right eye (Figs. 5 and 6). Intraocular pressures were 26 mm Hg in the right eye, and 10 mm Hg in the left eye. Gonioscopy showed open angles, grade III, without vascular abnormality. Goldmann perimetry in the right eye revealed an early arcuate scotoma with the I_4 test isopter and a nasal step defect. The left eye had a normal visual field. Outflow facility was 0.18 μl/min/mm Hg bilaterally. The right optic nerve head showed vertical elongation of the cup, but the left disk appeared normal and had a cup:disk ratio of 0.2.

Despite maximum medical therapy, including topical pilocarpine and epinephrine compounds, IOP increase of greater than 30 mm Hg persisted in the right eye. Because of early visual field and disk pathology, the right eye underwent filtration surgery. A posterior lamellar keratectomy was performed under a scleral dissection and corneoscleral limbus-based conjunctival flap. No excessive bleeding was encountered at surgery, and the patient did well postoperatively. Intraocular pressure has remained under 19 mm Hg without medication six months after operation.

Case 4—This 49-year-old white man was seen in consultation in 1976 for a superior branch-vein obstruction in the left eye. Visual acuity at that time was L.E.: 6/15 (20/50); R.E.: 6/4.5 (20/15). The right eye showed dilated episcleral vessels similar to those seen in the previous three cases (Fig. 7), but the left eye showed little if any vascular abnormality (Fig. 8). Intraocular pressures were 12 and 15 mm Hg respectively. Visual field examinations were normal bilaterally. Ophthalmoscopy revealed normal nerve heads, with cup:disk ratios of 0.2. Examination of the left fundus showed a lamellar hole and macular lipid consistent with a vascular occlusion. There was no family history of glaucoma. Medical examination failed to reveal any possible cause of the episcleral vascular anomaly.

DISCUSSION

We have described four patients with dilated tortuous episcleral vessels in the absence of carotid-cavernous-sinus disease. Three of these patients had documented open-angle glaucoma with characteristic disk and field changes. Cases 1 and 2 showed asymmetric onset of IOP increase which paralleled the degree of episcleral vascular abnormality present in each eye. Case 3 had unilateral glaucoma, ipsilateral to the more prominent vascular anomaly. Case 4 had no evidence of glaucoma. In none of these cases did gonioscopy reveal direct vascular involvement of the anterior chamber angle. In one patient (Case 2), blood was seen in Schlemm's canal, despite the IOP increase of 35 mm Hg.

Increased episcleral venous pressure may certainly inhibit normal aqueous outflow and increase the IOP.[1,9–11] Patients with carotid-cavernous-sinus fistula or obstructive orbital disease may show scleral engorgement and ipsilateral glaucoma.[1–4] Unilateral glaucoma may also occur with localized vascular abnormalities such as choroidal hemangiomatosis.[1,5,6,12]

In cases of obstructive orbital or cavernous sinus disease, increase in episcleral venous pressure and IOP are often concomitant, frequently despite normal facility of outflow.[1] On the other hand, cases of orbital hemangiomatosis do not characteristically show direct involvement of chamber angle structures by the vascular abnormality. Increased IOP

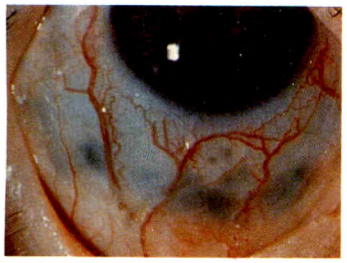


Fig. 1. Case 1. Right eye with dilated tortuous episcleral vessels.



Fig. 2. Case 1. Left eye with similar but less marked involvement of contralateral eye.

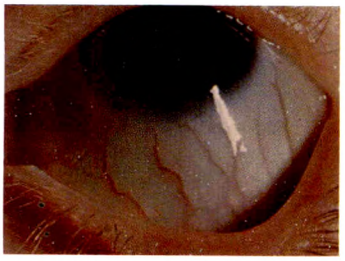


Fig. 3. Case 2. Dilated tortuous episcleral vessels of glaucomatous right eye.

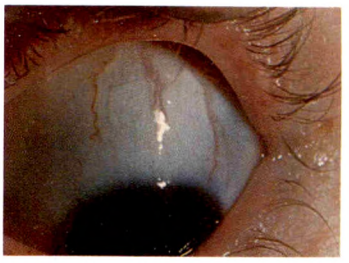


Fig. 4. Case 2. Left eye with less prominent episcleral vessel engorgement.

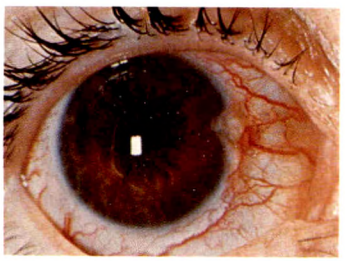


Fig. 5. Case 3. Tortuous dilated episcleral vessels of glaucomatous right eye.

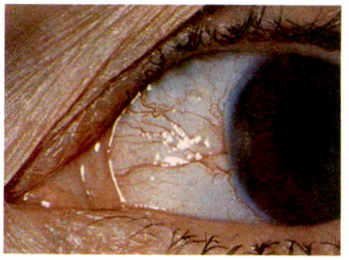


Fig. 6. Case 3. Left eye with less abnormal episcleral vessels and normal IOP.

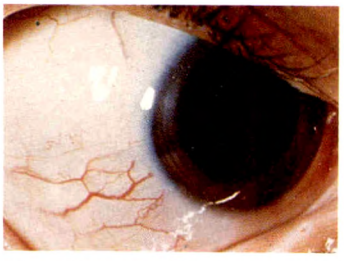


Fig. 7. Case 4. Dilated episcleral vessels of right eye.

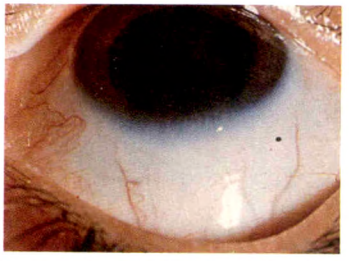


Fig. 8. Case 4. Minimal involvement of left eye with a few dilated vessels nasally.

(Radius and Maumenee)

often occurs with decreased facility of outflow and abnormalities of filtration structures similar to the occurrence in primary congenital glaucoma. Previous reports of patients with glaucoma and prominent episcleral vessels have usually documented abnormally high episcleral venous pressures.[9,10] Decreased values for facility of outflow have not been as consistent.

Because of technical limitations, episcleral venous pressures were not determined in these patients. However, in at least one case, blood reflux into Schlemm's canal, despite the increased IOP of 35 mm Hg, suggested that the episcleral venous pressure may have been increased as well. Alternatively, in all three cases with glaucoma (Cases 1-3), tonography revealed decreased facility of outflow in the involved eyes. Also, further decrease in outflow facility seemed to parallel the increases in IOPs. These observations suggest that the increase in IOP may not be directly related to episcleral vascular pathology, or that secondary changes in anterior segment structures may impede the aqueous outflow.

It is not clear whether these episcleral vascular abnormalities are congenital. In at least one patient, the vascular changes had been present from early childhood. In another, these vessels had been noted for at least the past ten years. Perhaps abnormal vasculature, present at birth, undergoes progressive dilatation until it is clinically apparent. Associated open-angle glaucoma may reflect increased episcleral venous pressure or coincident pathology in the trabecular tissue. Nevertheless, markedly dilated vessels bring these patients to the attention of the clinician, who must be aware of possible association with ocular hypertension. Furthermore, although they are characteristic of carotid-cavernous-sinus disease, the episcleral vascular anomalies may be unassociated with cranial or orbital vascular pathology.[9,10] Recognition of idiopathic dilated episcleral vessels may prevent unnecessary and potentially dangerous diagnostic procedures in otherwise healthy patients.

Summary

We studied four patients with idiopathic dilated episcleral vessels. Three of these patients had asymmetric or unilateral open-angle glaucoma in the eye with the greater degree of episcleral vascular anomaly. The fourth patient showed dilated episcleral vessels, but the intraocular pressure (IOP) was not increased. In the three patients with increased IOP, the facility of outflow was decreased. The episcleral venous pressure was not measured, but in one eye Schlemm's canal was engorged with blood despite an IOP of 35 mm Hg. We explored the possibility of a congenital vascular anomaly in the four cases.

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OCULODENTODIGITAL DYSPLASIA SYNDROME WITH ANGLE-CLOSURE GLAUCOMA

H. SAUL SUGAR, M.D.

Detroit, Michigan

Since the oculodentodigital dysplasia syndrome was first recognized by Lohmann[1] in 1920 and first described as such by Meyer-Schwickerath, Gruberich, and Weyers[2] in 1957, approximately 66 cases have been described in 40 families, including the present case. The occurrence of severe angle-closure glaucoma associated with microcornea in this case, and in the one I previously reported[3] emphasizes the importance of glaucoma in the syndrome, unlike the most recent reports that come from dentistry, oral surgery, pediatrics, and radiology.



Fig. 1 (Sugar). Facial appearance of patient showing typical nose and microcornea.

CASE REPORT

I first saw a 14-year-old girl in consultation in May 1975. Despite treatment since September 1968 for chronic narrow-angle glaucoma with 500 mg of acetazolamide twice a day and one drop of 1.5% carbachol four times a day, intraocular pressure was not controlled. The family history was noncontributory for glaucoma, but her paternal grandfather and paternal aunt, both deceased, had had small eyes. The patient's visual fields had shown large blind spots.

The patient's facial appearance was typical of the syndrome (Fig. 1), as were the fingers and toes. The fourth and fifth fingers of each hand showed clinodactyly (Fig. 2), as did both little fingers as manifested by medial curvature. The metacarpal bones of the first and fifth fingers were broad. The third, fourth, and fifth toes on both feet were incompletely segmented and lacked middle phalanges. The patient had had microdontia and marked enamel hypoplasia of the teeth as shown in plaster casts prepared before reconstruction by Dr. Samuel Glossman (Fig. 3). Roentgenograms of the spine were negative.

The horizontal diameter of the corneas measured R.E.: 10 mm; L.E.: 9 mm. Visual acuity was correctable to R.E.: 6/15 (20/50) (−4.00 sph.) and L.E.: 6/60 (20/200) (−3.25 sph.). Intraocular pressure was R.E.: 20 mm Hg; L.E.: 42 mm Hg. The right angle was narrow, but open with the iris root attached forward on the trabecular meshwork, as in some cases of congenital glaucoma. The left angle was almost entirely closed. The irides were normal. The disks were cupped in each eye with ratios of 0.5, right, and 0.7, left. I advised bilateral peripheral iridectomy and expected a trabeculectomy to be necessary on the left eye.

I saw the patient again in March 1976 after bilateral peripheral iridectomies and a trabeculectomy on the left eye. Her visual acuity was now R.E.: 6/15 (20/50); L.E.: finger counting. The left angle was blocked. Intraocular pressure as measured by applanation tonometry was 38 mm Hg in each eye. I advised filtration surgery on both eyes. A trephination was done on the right eye in April 1976 and another trabeculectomy was done in May. Perimetry on March 1, 1977, showed a field of 20 degrees in the left eye with scotomas located central-



Fig. 2 (Sugar). Appearance of fingers of both hands showing clinodactyly.

From Sinai Hospital of Detroit and Wayne State University School of Medicine, Detroit, Michigan.

Reprint requests to H. Saul Sugar, M.D., 14800 W. McNichols Rd., Detroit, MI 48235.

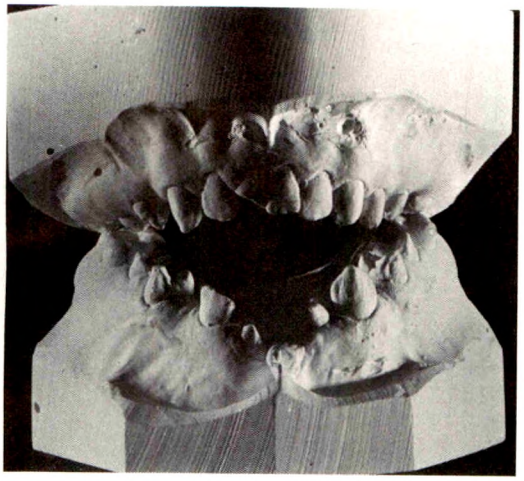


Fig. 3 (Sugar). Plaster casts of teeth showing microdontia and evidence of enamel hypoplasia.

ly and along both Bjerrum areas. The right field was normal except for an enlarged blind spot.

I saw the patient again in May 1977 when her corrected visual acuity was R.E.: 6/15; L.E.: light perception. She was taking 500 mg of acetazolamide at bedtime, one drop of 2% epinephrine three times a day, and one drop of 0.25% echothiophate iodide three times a day. Her intraocular pressure was R.E.: 32 mm Hg; L.E.: 50 mm Hg.

I performed a trabeculectomy on each eye. The operation was successful on the right eye, which had a pressure of 18 mm Hg without medication in August 1977. The operation on the left eye failed, but the eye was comfortable.

I[3] previously reported a case involving a 20-year-old white woman with the typical syndrome, including microphthalmos and syndactyly and clinodactyly. The horizontal diameters of the corneas measured 8 mm. The irides were normal. Intraocular pressure measured by applanation tonometry was R.E.: 21 mm Hg; L.E.: 20 mm Hg. I saw the patient seven years later, when she had bilateral acute glaucoma for which peripheral iridectomies were done. Both corneas were steamy, the conjunctivae were congested, and the intraocular pressure was approximately 60 mm Hg.

Discussion

The manifestations of the oculodentodigital syndrome may include: (1) a thin nose with hypoplastic alae and narrow nostrils; (2) hypotelorism or, occasionally, hypertelorism, often with medial epicanthus; small orbits and microphthalmos (6 to 10 mm corneal diameter), which may lead to glaucoma, as in my two cases; congenital cataract, secondary glaucoma, reduced eyelid aperture, persistent pupillary membranes, disk coloboma, strabismus, and optic atrophy; (3) bilateral syndactyly and camptodactyly of the fourth and fifth fingers (occasionally, the third finger also has ulnar clinodactyly); (4) hypoplasia of dental enamel and microdontia; oral defects including cleft of the soft and part of the hard palate and thickening of the alveolar ridge.

Other manifestations of the syndrome may include decreased head circumference; distorted ear pinnae; conduction deafness; hypotrichosis, or dry, lusterless hair that fails to grow to normal length; and hyperostosis of the skull. Intelligence is usually normal, but even when it is defective, there is only mild retardation.

Seven authors described family histories that suggest autosomal dominant heredity.[4–1] One other family had two affected siblings.[11] All other cases have appeared sporadically.

Summary

A 14-year-old girl with typical oculodentodigital syndrome had been treated for chronic glaucoma for seven years. She had corneas measuring R.E.: 10 mm; L.E.: 9 mm, with narrow angles open on the right, but almost entirely closed on the left. Gonioscopic examination of the right iris revealed that the root was attached forward on the trabecular meshwork, which suggested a congenital anomaly. Peripheral iridectomies were ineffective. In a case previously studied, a 20-year-old woman with typical oculodentodigital syndrome developed typical acute angle-closure glaucoma seven years after the original examination.

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OPHTHALMIC MINIATURE

The girl, who was long-sighted, took off her spectacles to look into the distance. He noticed that her eyes were very clear pale blue, paler than a harebell. And he noticed the smoothness of the skin round her eyes, like a petal, almost.

George Orwell, *Burmese Days*
New York, Signet, 1963

CLINICAL IMPLICATIONS OF AQUEOUS HUMOR STUDIES IN UVEITIS

RUDOLF WITMER, M.D.
Zurich, Switzerland

The aqueous humor has been the subject of intensive study for many years, although practitioners have not always been aware of the significance of aqueous humor analysis in the diagnosis of inflammatory diseases of the eye. De Grandmont[1] reported bacteriologic studies of the aqueous humor in cases of endophthalmitis as early as 1892, and Leber[2] began using diagnostic aqueous humor analysis at the turn of the century. In 1916 Brückner[3] published a paper on the cytology of the aqueous humor. The method of aqueous humor analysis I discuss herein was popularized by Amsler and Verrey[4] in the 1940s.

While Amsler was developing an anterior chamber puncture technique at Lausanne, the Irvines[5] examined the usefulness of aqueous humor studies as aids to the understanding of uveitis and related conditions. Unfortunately, they could not demonstrate any relationship between cell type in the aqueous humor and the etiology of the inflammation, or between the protein content and the type of uveitis.

In the decade following publication of their initial paper, Amsler and Verrey performed more than 3,000 anterior chamber punctures to obtain aqueous humor. Their findings appeared in Verrey's book, "Clinique de l'humeur aqueuse,"[6] and in a later report to the French Ophthalmological Society.[7] The description of aqueous cytology was as interesting as the results of bacteriologic studies[8] were disappointing. Contrary to his initial hypothesis, Verrey found that living microorganisms are rare in the inflamed eye. Von Sallmann, Locke, and Locke[9] confirmed the finding; aqueous taps in 88 of their cases of uveitis were bacteriologically negative. Furthermore, smear cytology provided no definite clue as to the etiology of the inflammation.

The perplexing absence of microorganisms in the aqueous humor led me to explore the hypothesis that the organisms are blocked by specific antibodies. Thus began my immunologic studies on the aqueous humor. Immunology in 1947 was a simple science; it encompassed some knowledge of skin reactions and humoral antibodies, but the important distinction between cellular and humoral immunity had not yet been made. Consequently, we naively expected that circulating antibodies should be present in every case of endogenous uveitis.[10]

Woods[11] studied the etiology of uveitis extensively, principally through skin tests that used many different types of antigen. In 1957,[12] he discussed the problem of lens-induced uveitis and stated that all patients with endophthalmitis phacoanaphylactica were hypersensitive to lens protein, which skin test reactions showed. Additionally, he examined heterochromic cyclitis, but overlooked the possibility of aqueous humor studies in both that inflammation and in endophthalmitis phacoanaphylactica.

Hogan, Kimura, and O'Connor[13] developed a thorough clinical examination for uveitis patients. Hogan, Wood, and Godfrey[14] also conducted cytological studies, some with electron microscopy. Unfortunately, they were unable to find either bacteriologic or viral inclusions in any of the cells examined.

Patients suffering from uveitis are, as a rule, remarkably healthy, and system-

From the Department of Ophthalmology, University of Zurich, Zurich, Switzerland.
Reprint requests to Rudolph Witmer, M.D., University Eye Clinic, CH-8091 Zurich, Switzerland.

ic examination is generally unrewarding. Most patients, except those with Behçet's disease or sarcoidosis, do not show signs of systemic disease. This may explain the frequency of negative serum findings in uveitis, despite sophisticated immunologic tests.

Nothing seems more natural for the internist or for the surgeon than to puncture or perform a biopsy of the organ in which disease is suspected. By contrast, the ophthalmologist looks for changes in the blood, in the urine, or in organs other than the eye when there is ocular disease. He generally does not dare puncture the eye, examine the products of inflammation in the aqueous humor, or take biopsy specimens of inflamed ocular tissue. Anterior chamber paracentesis is a completely safe procedure if done under normal aseptic conditions by an experienced person.

Material and Methods

Between 1968 and 1976 our laboratory analyzed 945 serum samples and 693 paired samples of serum and aqueous humor. We routinely carried out the following serologic tests: (1) Middlebrook-Dubos test for tuberculosis; (2) antistreptolysin-O test; and (3) *Toxoplasma* dye test (superceded in 1970 by the immunofluorescence test). In selected cases, we performed complement fixation tests for herpes simplex virus, herpes zoster virus, mumps virus, and adenovirus. Serum and aqueous humor protein contents were determined photometrically. Over the last four years we have also procured iris specimens during surgery for glaucoma or cataract secondary to uveitis.

In our laboratory analyses we call the antibody concentration relative to gammaglobulin content or to total fluid protein content "antibody activity." We define the ratio of aqueous humor antibody activity to serum antibody activity as the ratio of antibody activity. If the antibodies present in the aqueous humor are solely due to leakage of immunoglobins through the blood-aqueous barrier, the ratio of antibody activity is less than 1.0. Conversely, a ratio equal to or higher than 1.0 suggests local antibody formation.

This method has worked well in cases showing a marked increase in the protein content of the aqueous humor, that is, in a markedly inflamed eye. In the absence of inflammation of the anterior segment, such as in posterior uveitis or in chorioretinitis, the test is inaccurate.

Results

One third of the 945 routine examinations of serum antibody content showed no positive test for any suspected antibody. The remaining tests showed a variety of results (Table 1). Tuberculosis and toxoplasmosis studies showed similar findings, about 50% of the tests being positive for each. There was no significant difference between cases of anterior and posterior uveitis. More than 94% of the antistreptolysin tests were negative; in contrast, 90% of the viral antibody tests in uveitis patients were positive.

We conducted tests on 693 pairs of serum and aqueous humor. Of these, 215 had positive aqueous humor results for various antibodies. However, the majority of these had antibody activity ratios less than 1.0, which, presumably, indicates a leakage of protein through the inflamed ciliary body. In 63 eyes there was local antibody formation, as evidenced by antibody activity ratios greater than or equal to 1.0. As shown in Table 2, local antibody activity is suggested in toxoplasmosis and in certain viral diseases.

Among the patients who showed a positive ratio of antibody activity for toxoplasmosis, five had ratios close to 1.0. Three of them were children with a typical chronic anterior uveitis, band-shaped keratopathy, and cataract. Such a picture suggests juvenile polyarthritis, although congenital toxoplasmosis without posterior ocular lesions is possible. The remain-

TABLE 1

SEROLOGIAL RESULTS IN UVEITIS PATIENTS

Diagnosis	Total Cases	All Tests Negative (No. of Cases)	Tuberculosis +	Tuberculosis −	Toxoplasmosis +	Toxoplasmosis −	Anti-streptomycin +	Anti-streptomycin −	Virus +	Virus −
Diffuse uveitis	155	61	33	33	31	40	4	55	49	4
Iritis, iridocyclitis	138	43	39	34	30	50	3	69	43	9
Chronic cyclitis	80	20	24	28	18	35	1	46	39	6
Chorioretinitis	159	68	38	24	49	35	4	55	35	2
Juxtapapillaris	29	8	6	7	12	7	0	13	12	0
Centralis	75	31	23	16	13	31	5	30	15	1
Disseminated	17	5	6	6	4	7	0	10	8	0
Others	191	57	31	25	34	37	5	47	75	7
Unknown	101	32	12	12	18	14	1	19	36	2
Total	945	325	212	185	209	256	23	344	312	31
			397		465		367		343	

ing 32 patients had antibody activity ratios ranging from 1.5 to 100. Fifteen patients suffered from a severe recurring panuveitis, some with large, well-established foci in the fundus as well as new satellite lesions, massive vitreal opacities, and extensive involvement of the anterior segment. Some of the patients had low serum titers (1:16 to 1:32), which are not inherently diagnostic (Table 3).

Twenty-six patients had positive complement fixation tests for viral diseases (Table 4). Antibodies directed against herpes simplex were found in 18 cases; only in ten was the etiology evident on morphological grounds alone. Five patients were suffering from acute iritis. Among five patients presumed to have Behçet's syndrome, only one showed evidence of antibodies against herpes simplex; the others were serologically negative. One patient with Vogt-Koyanagi syndrome had iridocyclitis and an exudative retinal detachment; the titer of the subretinal fluid for herpes simplex antibodies was 1:1024. We diagnosed herpes zoster in three cases, one of which showed typical keratouveitis following skin involvement.

Adenovirus type 8 may produce uveitis, and we saw one case of acute iritis that appeared one week after an influenza-like systemic illness. Another patient developed a typical chronic cyclitis with severe

TABLE 2

LOCAL ANTIBODY ACTIVITY IN 63 CASES WITH AN ANTIBODY ACTIVITY RATIO OF 1.0 OR MORE

Antibody Activity	No. of Cases
Tuberculosis	0
Streptococcal diseases	0
Toxoplasmosis	37
Viral diseases	26

TABLE 3

37 CASES OF UVEITIS WITH HIGH ANTIBODY ACTIVITY-RATIO FOR TOXOPLASMOSIS

	Ratio 1.0	Ratio 2-10	Ratio Over 10
Iritis	4	2	1
Iridocyclitis		3	
Chronic cyclitis		2	
Chrioretinitis			
Localized	1	5	
Disseminated		2	2
Panuveitis		10	5
Total cases	5	24	8

TABLE 4

26 CASES OF UVEITIS WITH HIGH ANTIBODY ACTIVITY RATIO FOR VIRUS.

	Positive Ratio			
	Herpes simplex	Herpes zoster	Mumps	Adeno-virus
Iritis	7	2	1	1
Iridocyclitis	4		1	
Chronic cyclitis	2			1
Chorioretinitis				
Localized				
Disseminated				
Panuveitis	5*	1	1†	
Total cases	18	3	3	2

*Behçet's disease.
†Sympathetic ophthalmia.

vitreous opacities and macular edema. One patient with sympathetic ophthalmia had tested positive for mumps virus.

In ten patients we collected aqueous humor samples before intraocular surgery. From these patients, we retrieved iris specimens for electron microscopy. In five of the patients we were able to make presumptive clinical diagnoses (Table 5); three of the remaining patients had positive ratios for herpes simplex virus antibodies. The electron microscopic findings in all cases were fairly consistent, and we invariably found cells compatible with an immunologic reaction: macrophages, lymphocytes, and mast and plasma cells. We previously reported such findings in a case of chronic cyclitis with secondary glaucoma.[15] No virus particles appeared in the iris in any of the presumptive herpes simplex cases, in contrast to a case in which we found herpes virus particles in the iris.[16]

DISCUSSION

Even in tuberculosis, which is one of the best examples of a cell-mediated immunologic reaction, the likelihood that large amounts of circulating humoral antibodies are produced is remote. Thus tests such as Middlebrook-Dubos have little diagnostic value. However, carefully performed quantitative serology may

TABLE 5

RESULTS OF ULTRASTRUCTURAL STUDIES ON TEN IRIS BIOPSIES

Diagnosis	No. of Cases	Serology	Electron Microscopy
Infantile anterior uveitis	1	Negative	Macrophages; fibrosis
Behçet's disease	1	Negative	Mast cells; endothelial cell damage
Recurrent uveitis and spondylarthritis	1	Negative	Infiltration with lymphocytes and plasma cells
Recurrent uveitis chorioretinal scar	1	Toxoplasma ratio 100	Mast cells; lymphocytes
Chronic uveitis Boeck's sarcoidosis	1	Negative	Lymphocytes; plasma cells
Chronic uveitis undetermined	2	Negative	Mast cells; plasma cells; lymphocytes
Chronic cyclitis	3	Herpes simplex virus ratio 1:4	Plasma cells; lymphocytes

still be helpful in pinpointing tuberculosis as the cause of a particular case of uveitis.

If a specific antigen (for example, tubercle bacillus antigen) enters the uvea, transformed B-lymphocytes and plasma cells may generate local antibodies there. Humoral antibodies may also appear in the aqueous humor and in the vitreous, and they may also be present in the blood. If the focus of immune activity is local, one may expect the relative concentration of antibody in the aqueous humor to be higher than that in the serum. (Experimental data have confirmed that the uvea may act like a lymph node and produce local accumulations of antibodies.[15])

As we had anticipated, serum samples alone gave little if any information about the etiology of uveitis. Tuberculosis is a well controlled disease that rarely reaches the stage in which hematogenously disseminated organisms can be found. The diagnosis of disseminated chorioretinitis as tuberculous in origin remains presumptive. The clinician should also remember that a positive response to therapy is not necessarily indicative of the cause of uveitis, as many chorioretinal lesions heal within two to six months without treatment.

Nodular uveitis is generally considered pathognomic for sarcoidosis. There is as yet no test available to confirm Boeck's sarcoid, with the possible exception of conjunctival or iridal biopsy.

Antistreptolysin-O titers were negative in 94% of our patients. Presumably, beta hemolytic streptococci (group A) play almost no role in the production of uveitis. However, many streptococcal infections may be overlooked because there is no specific test for them. It might be possible to return to the multiple skin testing method of Woods, which provides a presumptive diagnosis of streptococcal uveitis. Our clinical observations of exudative chorioretinitis and the response of these patients to high-dose penicillin therapy suggest that some of the monofocal, acute chorioretinal lesions we observed with severe vitreal reaction may be the result of focal infection with pyogenic pathogens susceptible to penicillin therapy.

Toxoplasma dye test titers limited to serum testing are meaningless, and their results are uniformly distributed among the uveitis patient population. Based on clinical experience, we would tend to disregard a positive titer in a patient with iritis, but pay more attention to a positive titer in a patient with chorioretinitis. The presence of diffuse severe uveitis seems to justify paracentesis. At least 5% of our severe uveitis cases were toxoplasmic; among patients with posterior uveitis, the percentage may be still higher.

Viral infections are common today, and their ophthalmic significance may be greater than is presently realized, particularly in hitherto unrecognized uveitis syndromes (over 4% in our series). The distinction between herpes simplex infection and herpes zoster infection requires use of a complement fixation test. Even electron microscopy cannot distinguish between these infections.

No case of isolated chorioretinal disease occurred in our group of virus-associated disease. This confirms the clinical impression that viral disease is generally restricted to the anterior segment. However, seven cases of diffuse uveitis of presumed viral etiology had serious involvement of the vitreous.

In addition to immunologic testing, we conducted electron microscopic examinations on ten specimens. These did not provide any new data on the status of the aqueous humor. Ultrastructural studies of iris specimens showed a marked accumulation of immunologically active cells. Lymphocytes (probably of both the B and T types) and many plasma cells were present. The plasma cells must produce some antibody, and it is indeed frustrating not to be able to detect it. We saw many macrophages, presumably loaded

with antigen; mast cells with histamine-containing granules and platelets adhering to the damaged endothelium of inflamed capillaries; widespread cell destruction; and fibrosis with collagen formation—all of which would indicate an immunologic reaction.

Of 693 paired samples of serum and aqueous humor tested, 63 showed high levels of antibody activity in the aqueous humor. This is a little less than 10%. Therefore, over 90% of our uveitis patients did not derive any benefit from their anterior chamber punctures. Because technical capabilities prevented us from performing more than five serologic tests on any one sample of approximately 0.2 ml of aqueous humor, we selected those tests most likely to give a positive result on the basis of the clinical appearance of the lesion. This choice may be misleading. Among our patients, we encountered typical diseases such as toxoplasmic chorioretinitis or herpetic keratouveitis, but these findings do not exclude other clinical pictures. Thus the thorough observation and documentation of the findings on a given uveitis patient constitute only one side of the story. Careful examination may lead to an accurate diagnosis, but almost never to a certain etiology. If we were able to run up to 20 serologic tests on the same 0.2 ml of aqueous humor, we would probably obtain additional useful information.

Despite limited returns, aqueous humor studies are still justified because in most uveitis patients, the eye is apparently the only diseased organ of the body. Additional testing is needed to determine the complement content in cases of suspected immune complex disease. We should also work toward the perfection of tests for the detection of specific lymphokines of T-cell origin as well as of antibodies of B-cell origin. One potential aid in the attainment of these goals may be the use of peroxidase to label the various antigens used in testing iris specimens.

SUMMARY

We studied the serologic findings in serum and aqueous humor samples from 693 cases of uveitis. Specimens were tested for the presence of humoral antibodies against tuberculosis, toxoplasmosis, antistreptolysin-O, herpes simplex and herpes zoster viruses, mumps virus, and adenovirus. Serologic analyses rarely indicated tuberculous or streptococcal infections, but frequently showed toxoplasmosis and viral diseases.

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RETINAL DEPRESSION SIGN INDICATING A SMALL RETINAL INFARCT

MICHAEL H. GOLDBAUM, M.D.
San Diego, California

While examining patients with homozygous sickle cell disease (hemoglobin SS), sickle cell-hemoglobin C disease (hemoglobin SC), and sickle cell-thalassemia disease (hemoglobin S-thal), I observed alterations of the retinal reflex that resembled extra foveal pits. Subsequent examination has shown that these lesions are depressions in the surface of the retina caused by focal tissue loss and thinning of the retina. Since the discovery of these depressions in the retinas of patients with various sickling hemoglobinopathies, I have found similar depressions in three white patients with systemic hypertension, with retinal arteriolitis, and with juvenile onset diabetes mellitus.

SUBJECTS AND METHODS

At the Sickle Cell Eye Clinic at the University of Illinois Eye and Ear Infirmary, 42 patients with hemoglobin SS, SC, and S-thal without retinal neovascularization (preproliferative sickle retinopathy) have been longitudinally studied for three years of a projected five-year period. Another group of 41 patients with hemoglobin SS, SC, S-thal, hemoglobin C trait (hemoglobin AC), and sickle cell trait (hemoglobin AS) who have retinal neovascularization (sea fan formation) are being observed in a treatment series.[1,2] Three patients had one eye each in each group. Hence, the total number of patients was 80. I characterized the retinal depression sign on the basis of findings in these patients with sickle hemoglobinopathies, although the depressions found in white patients with other conditions had similar characteristics.

The retinal depressions are most easily seen by indirect ophthalmoscopy. Within the light reflecting from the internal limiting lamina, they appear as dark areas with a central bright spot or streak (Fig. 1). Normally, the examiner holds the lens of the indirect ophthalmoscope so as to minimize the reflections from the internal limiting lamina. These reflections often partially obscure fundus details, and the habit of most ophthalmologists is to ignore or eliminate these reflexes. However, if the examiner positions the indirect ophthalmoscope lens to maximize the reflexes, the depressions stand out starkly from the reflexes (Fig. 1).

The depression edges appear dark because the sloping borders of the internal limiting lamina reflect the light away from the observer (Fig. 2). Because the internal limiting lamina surface is often concave within the depression, the light reflecting off the internal limiting lamina focuses to a point, forming a real image of the light in the center of the depression in the vitreous chamber anterior to the retina (Fig. 2). The large depressions have a flat bottom and do not produce a point of light as do the small depressions (Fig. 3).

As the examiner moves the condensing-imaging lens of the indirect ophthalmoscope, the point of focus in the vitre-

From the Department of Ophthalmology, University of Illinois Eye and Ear Infirmary, Chicago, Illinois. This work was supported in part by Contract 72-2956B and Grant PHS HL 15168-05 from the National Heart and Lung Institute to the Department of Ophthalmology, University of Illinois Eye and Ear Infirmary, Chicago, Illinois.

Reprint requests to Michael H. Goldbaum, M.D., Division of Ophthalmology, University of California, San Diego, 3350 La Jolla Village Drive, San Diego, CA 92161.

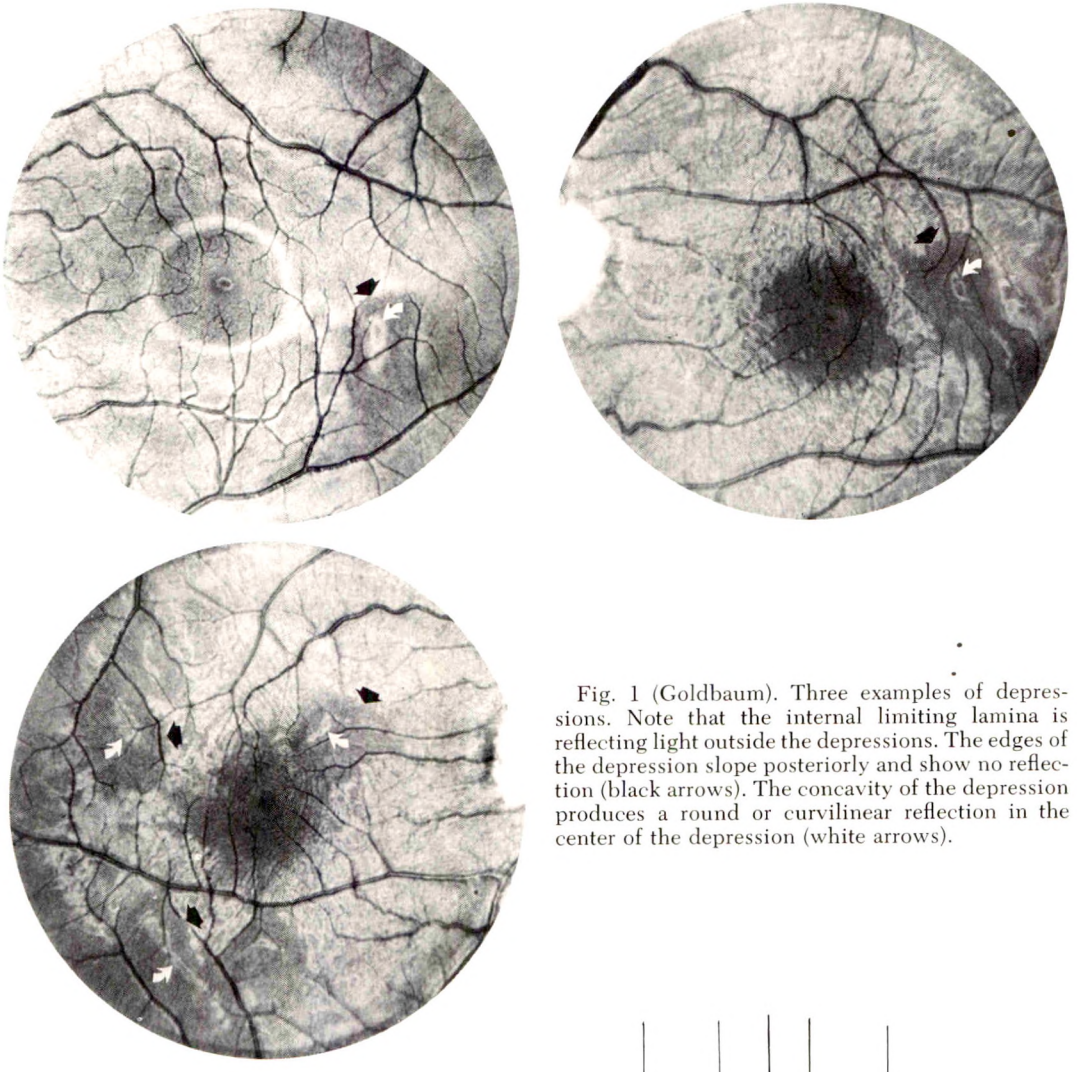


Fig. 1 (Goldbaum). Three examples of depressions. Note that the internal limiting lamina is reflecting light outside the depressions. The edges of the depression slope posteriorly and show no reflection (black arrows). The concavity of the depression produces a round or curvilinear reflection in the center of the depression (white arrows).

ous chamber moves in the opposite direction. Because the examiner sees an inverted image of the retina, the point of light appears to move in the same direction as the examiner's hand—with motion (Fig. 4).

The borders of the depression are easily defined by moving the condensing-imaging lens. They may be as small as 100 μ or larger than 1,500 μ. It is difficult to delineate the edges of an infarct larger than 3,000 μ (2 disk diameters). The de-

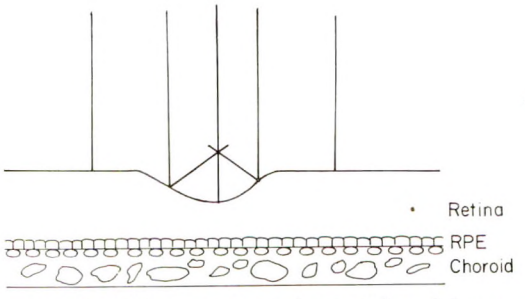


Fig. 2 (Goldbaum). Optical principles of depression. Light reflecting off internal limiting lamina away from depression returns to observed. Light reflecting off sloping internal limiting lamina at edge of depression reflects away from observer. Concave surface of depression produces point or line of light at intersection of reflecting light rays. RPE indicates retinal pigment epithelium.

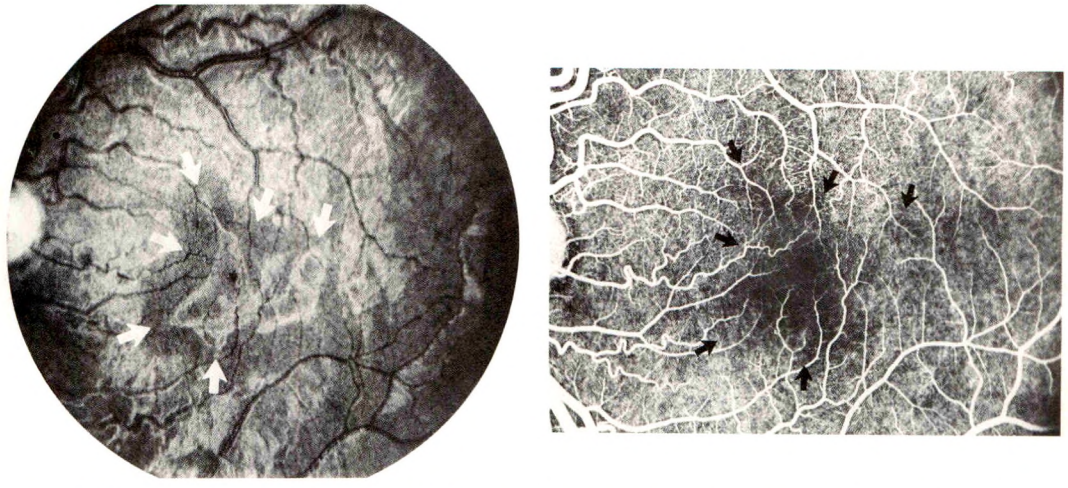


Fig. 3 (Goldbaum). Left, Depression partially involves fovea. Arrows in same location in left and right parts of figure. Large depression with flat bottom does not produce central point or streak of light. Right, Corresponding fluorescein angiogram shows decreased density of capillary net. Note similarity in shape.

pressions are most easily seen in the macular and paramacular retina, as reflections outside this region are hard to elicit.

The retinal reflexes and the depressions may be visible in patients of any age, although they are easier to see in younger patients with pigmented fundi. Attempts to photograph the depressions become increasingly difficult the older the patient; beyond age 30, the depressions, though ophthalmoscopically visible, often cannot be photographed.

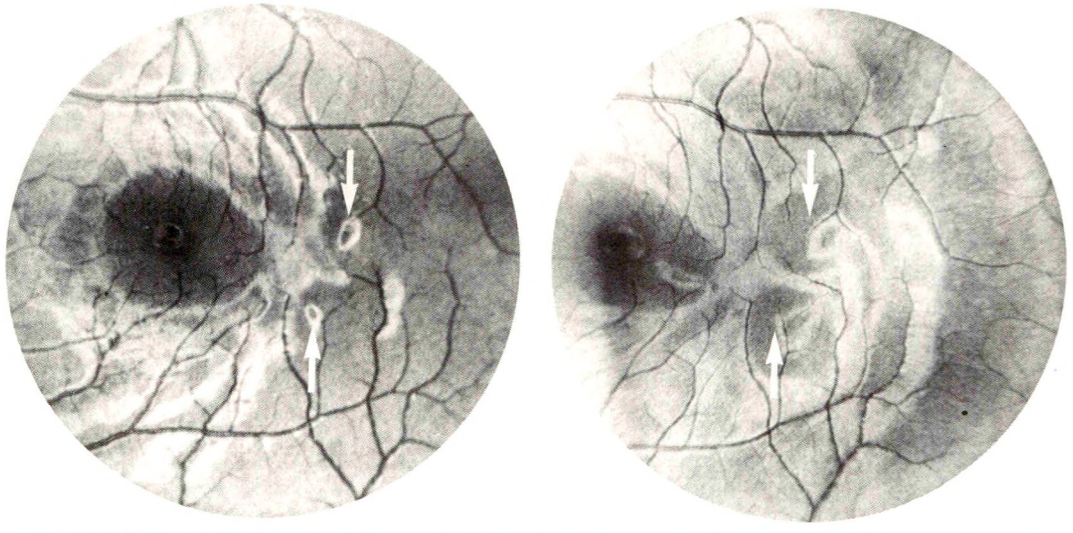


Fig. 4 (Goldbaum). Movement of the condensing-imaging lens of the indirect ophthalmoscope causes the light in center of depression to move the same direction as the lens—with motion. Paired arrows show this motion. Lens moves from left in Figure 4, left, to right in Figure 4, right.

Patients exhibiting the retinal depressions underwent complete eye examinations. The border of each depression was carefully drawn. Amsler grid tests were performed with both the grid and the dot pattern. Kinetic visual fields were examined by using the Goldmann perimeter through undilated pupils. The Goldmann static perimeter tested static perimetry along the meridian passing through the center of the depression. The patients with hypertension, retinal arteriolitis, and diabetes were similarly examined.

When the depressions were photographed, the photographer adjusted the camera to catch the maximum reflection from the internal limiting lamina. On fluorescein angiography, slightly varying the focus of the camera over several pictures insured capturing capillary detail.

Results

Sixteen of the total 80 patients (20%) with sickle hemoglobinopathy had depressions in the posterior pole (Table 1). Thirteen of 24 patients with hemoglobin SS (54%) had depressions, and one patient of ten with hemoglobin S-thal had depressions (10%) (Table 2). The patients' ages ranged from 11 through 39 years (mean 24.5 years). Nine were male and seven female.

In addition to the 16 patients with sickling hemoglobinopathies, three patients with normal hemoglobin (hemoglobin AA) had depressions. One patient was a 48-year-old white woman with systemic hypertension, another was a 32-year-old white woman who had retinal arteriolitis,[3] and the third was a 24-year-old white woman with juvenile onset diabetes mellitus.

In the 19 patients, 34 eyes had depressions; 15 patients had depressions bilaterally and four unilaterally. The visual acuity of most of the eyes ranged from 6/6 (20/20) to 6/9 (20/30). Only two eyes had visual acuity of 6/4.5 (20/15), although such a young group of patients might be expected to yield a much higher proportion with visual acuity of 6/4.5 (20/15). One patient had macular depressions more than 2 disk diameters wide with a zone of macular nonperfusion of comparable size in each eye. His visual acuity was finger counting in one eye and 6/120 (20/400) in the other.

Static perimetry consistently showed an absolute scotoma in the region of the depression. These field defects were as small as 1 degree; consequently, the patients usually did not discern the scotomas on kinetic perimetry (Figs. 5-8). Although the visual acuity in the patients with depressions was normal or mildly reduced, the sensitivity of the fixation point on static perimetry was markedly reduced when the depression connected with the fovea (Fig. 8). The patients with a normal macula were able to see a 0.25-mm^2 spot at fixation about 1.25 to 1.6 apostilbs above the background illumination (Fig. 9), whereas the patients with depressions close to the macula had reduced sensitivities up to 15 apostilbs above the background.

Surprisingly, only five patients noted a scotoma on the Amsler grid, four unilaterally and one bilaterally. One eye had 6/4.5 (20/15) and three eyes had 6/7.5 (20/25) visual acuity. The patient with visual acuities of 6/60 (20/200) and finger counting demonstrated a large scotoma in both eyes. All scotomas were negative; no positive scotomas were observed.

Case report

A 26-year-old black woman (Case 15, Table 1) with hemoglobin SC disease had sea fans (peripheral retinovitreal neovascularization) in the left eye. The patient was treated on Feb. 21, 1974, with cryopexy to the sea fans in the left eye, after which the eyes were observed daily for a week. On Feb. 27, cotton-wool spots had just developed in the posterior pole of the untreated right eye (Fig. 10, top left

TABLE 1

SUMMARY OF PATIENT DATA EYES WITH DEPRESSIONS

Case No.	Age, (yrs)	Sex	Hb	Visual Acuity	Amsler	Comment
1	36	F	AA	R.E.: 6/7.5 (20/25)	No scotoma	Occlusive retinal arteriolitis
				L.E.: 6/6 (20/20)	No scotoma	
2	39	F	AA	L.E.: 6/9 (20/30)	Uncertain scotoma	Hypertension
3	24	F	AA	L.E.: 6/6– (20/20–)	No scotoma	Juvenile onset diabetes mellitus
4	36	M	SS	R.E.: 6/4.5– (20/15–)	No scotoma	
				L.E.: 6/6 (20/20)		
5	21	M	SS	R.E.: 6/6 (20/20)	No scotoma	
				L.E.: 6/6 (20/20)	No scotoma	
6	36	F	SS	R.E.: 6/6 (20/20)	No scotoma	
				L.E.: 6/6 (20/20)	No scotoma	
7	18	M	SS	R.E.: 6/6 (20/20)	No scotoma	
				L.E.: 6/6 (20/20)	No scotoma	
8	23	M	SS	R.E.: 6/6 (20/20)	No scotoma	Cerebrovascular accident
				L.E.: 6/7.5 (20/25)	No scotoma	
9	17	M	SS	L.E.: 6/7.5 (20/25)	No scotoma	
10	11	M	SS	R.E.: 6/7.5– (20/25–)	Scotoma corresponding to depression	Cerebrovascular accident and mental retardation
				L.E.: 6/9 (20/30)	No scotoma	
11	17	F	SS	R.E.: 6/7.5 (20/25)	No scotoma	
				L.E.: 6/9 (20/30)	No scotoma	
12	17	F	SS	R.E.: 6/7.5 (20/25)	No scotoma	
				L.E.: 6/9 (20/30)	No scotoma	
13	26	M	SS	R.E.: 6/60 (20/200)	Large scotoma	Optic atrophy
				L.E.: CF	Large scotoma	Optic atrophy
14	17	F	SC	R.E.: 6/6 (20/20)	No scotoma	
				L.E.: 6/4.5– (20/15–)	Scotoma corresponding to depression	
15	31	M	SC	L.E.: 6/6 (20/20)	No scotoma	
16	26	F	SC	R.E.: 6/9 (20/30)	No scotoma	
				L.E.: 6/6 (20/20)	No scotoma	
17	29	F	SC	R.E.: 6/7.5 (20/25)	No scotoma	
				L.E.: 6/7.5 (20/25)	No scotoma	
18	37	F	SC	R.E.: 6/7.5 (20/25)	No scotoma	
				L.E.: 6/7.5 (20/25)	Scotoma corresponding to depression	
19	27	M	S-thal	R.E.: 6/7.5 (20/25)	No scotoma	
				L.E.: 6/7.5 (20/25)	No scotoma	

and right). Fluorescein angiograms of the right eye showed an arteriolar occlusion with capillary nonperfusion at the site of each cotton-wool spot. One of these focal areas of nonperfusion broke through the capillary net bordering the foveal avascular zone. The cotton-wool spots faded, and over the ensuing six months, the focal zones of arteriolar occlusion and capillary nonperfusion partially reperfused. In place of each cotton-wool spot, a depression in the retinal surface appeared (Fig. 10, bottom left and right).

The fluorescein angiogram in August 1974 showed that the occluded arterioles and capillary beds of the right eye were perfusing. Except within the depression penetrating the border of the foveal avascular zone, the only other abnormality in the

TABLE 2

INCIDENCE OF DEPRESSION IN A SELECTED GROUP OF PATIENTS WITH SICKLING HEMOGLOBINOPATHIES

Hemoglobin Type	SS	SC	S-thal	AS	AC	Total
Sample size	24	43	10	2	1	80
Depression	13	2	1			16
Proportion with depressions	54%	5%	10%			20%

fluorescein angiogram was a focal decrease in the density of capillaries in each depression site (Fig. 10, bottom left and right). The depression bordering the foveal avascular zone did not fully reperfuse, although at six months some vessels were growing in from the lesion edge. The patient's visual acuity in the right eye before and after the infarcts was 6/6 (20/20), even though the edge of the foveal avascular zone had been breached.

Subsequent complications arising from retinal neovascularization and its treatment in this eye have caused severe scarring in the macula. Hence, test of

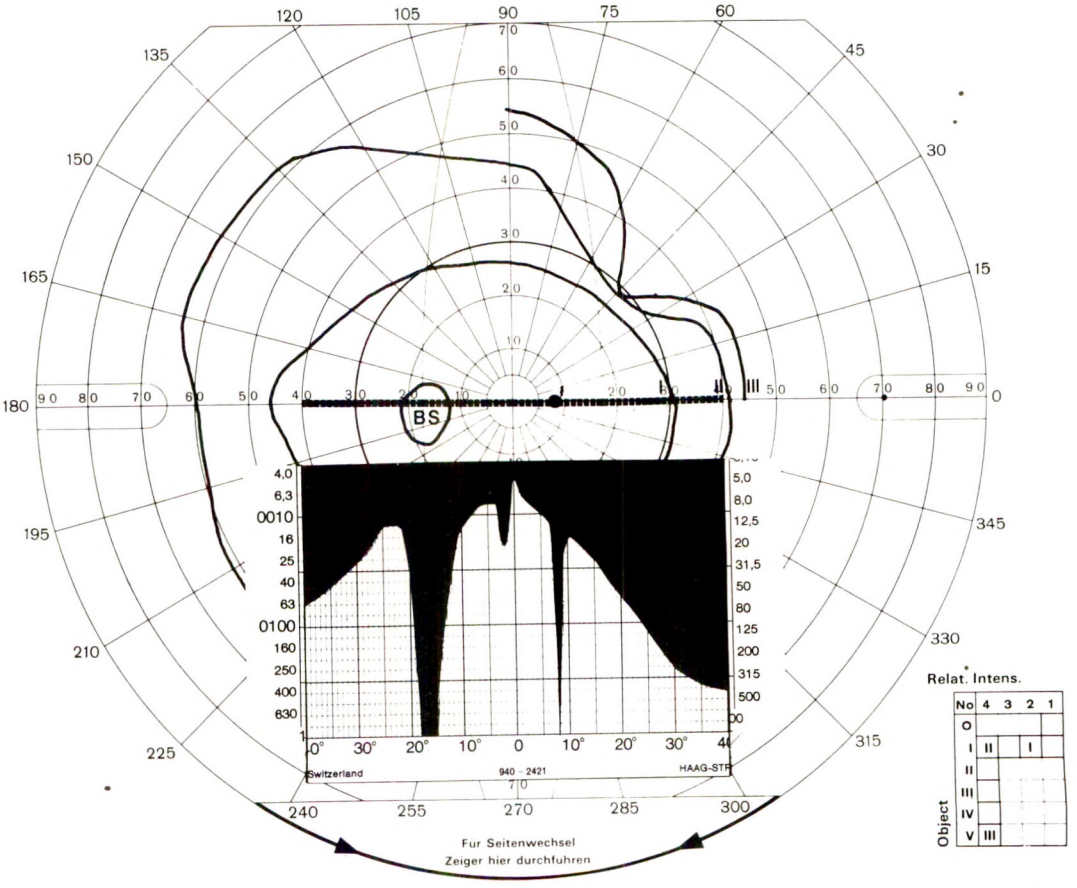


Fig. 5 (Goldbaum). Kinetic and static perimetry. Small depression gave visual field defect that could be found only by kinetic perimetry. Visual acuity was 6/6 (20/20).

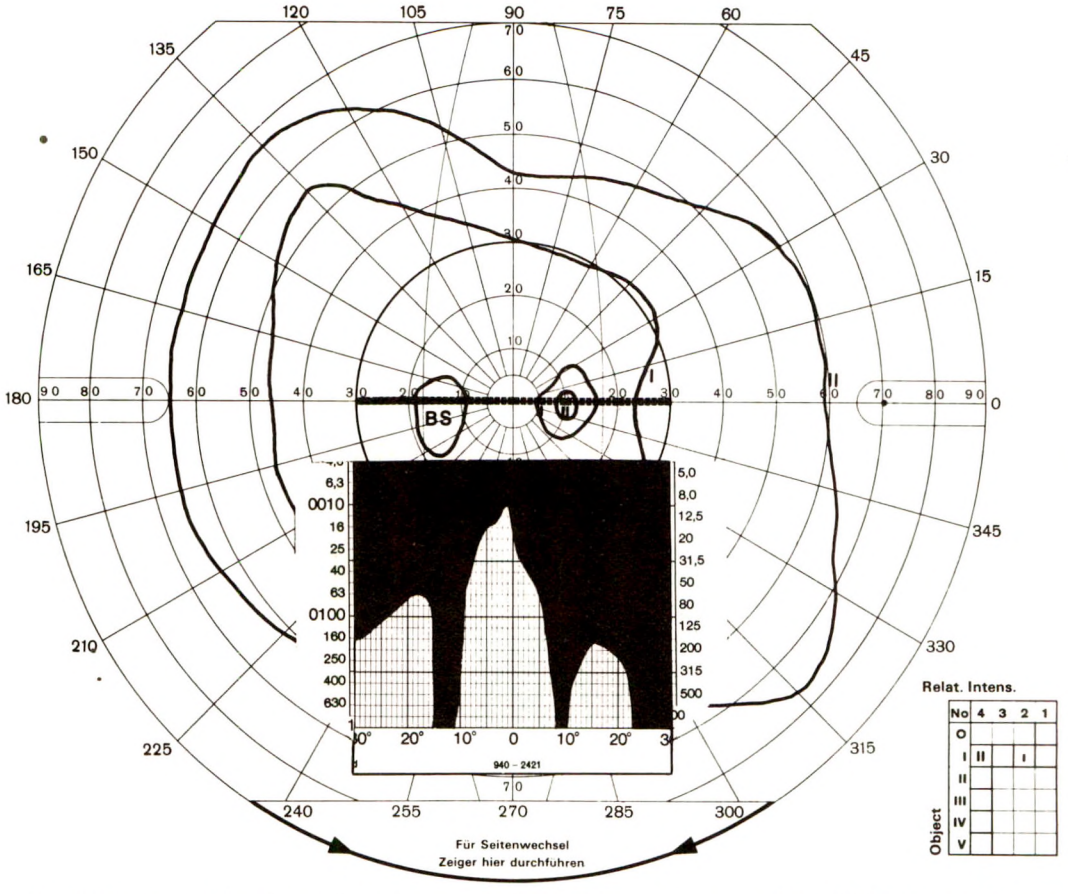


Fig. 6 (Goldbaum). Moderate-sized depression shown in Figure 3 produced focal field defect on kinetic perimetry. In addition to the absolute scotoma temporal to fixation found by static perimetry, there is considerable reduction of fixation sensitivity. Visual acuity was 6/7.5 (20/25). Depression involved the fovea.

visual fields, static fields, and Amsler grid were not performed.

Discussion

Light reflecting from the internal limiting lamina was recognized shortly after the introduction of the ophthalmoscope in 1851. Most physicians are familiar with such physiologic reflexes as the perimacular oval, the point of light from the foveal pit, or the streak of light from the cylindrical surface of retinal blood vessels. Less well known physiologic reflexes are the Weiss reflex[4] around the optic nerve head, and Gunn's dots,[5] thought to be light reflecting from tiny irregularities of the internal limiting lamina where Müller's fibers insert. Ballantyne and Michaelson[6] have described annular reflexes around a choroidal scar. An annular reflex at the junction of the concave surface of the attached retina often marks the location of central serous retinopathy. The retina depression sign occurs from the concavity of the inner retinal surface produced by a retinal infarct usually smaller than 2 disk diameters in size.

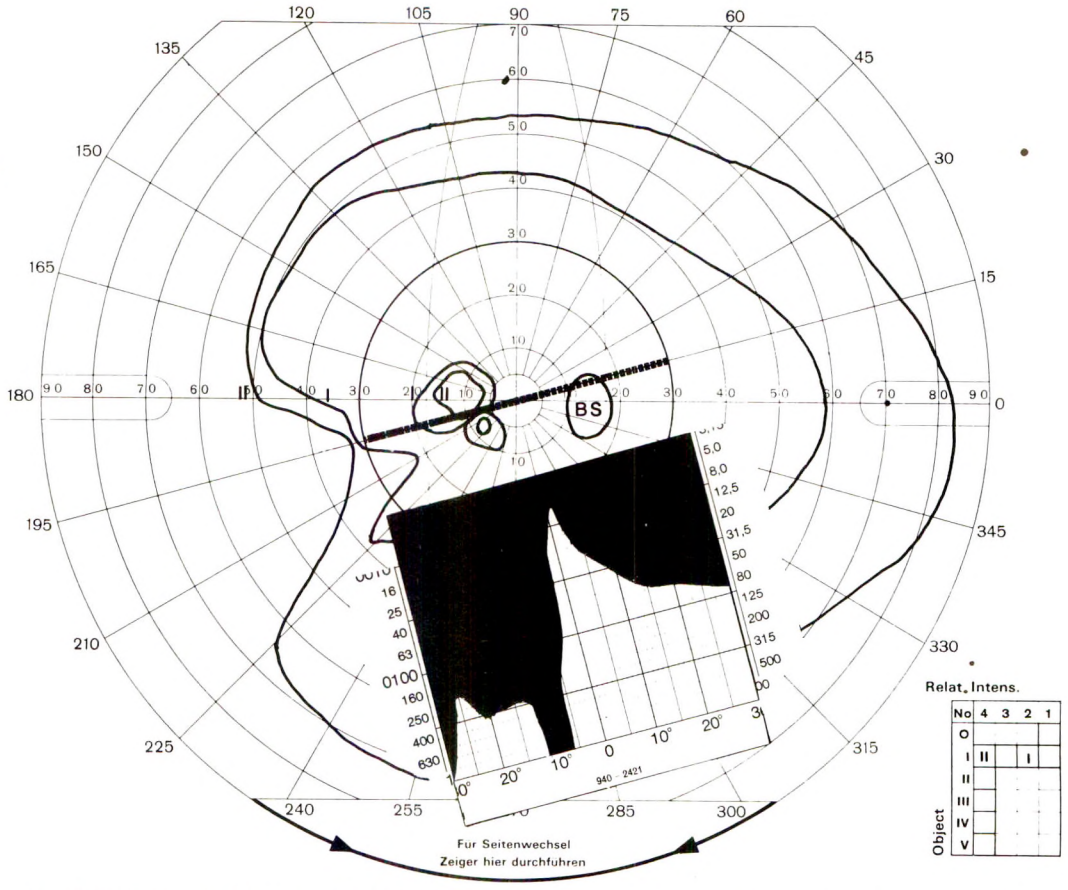


Fig. 7 (Goldbaum). Moderate-sized depression produced sufficient nerve fiber deficiency to cause focal contraction of the peripheral field. Visual acuity was 6/7.5 (20/25).

The fluorescein angiogram may show a decreased density of capillaries corresponding to the area of retinal depression (Fig. 3). On the other hand, the area with retinal depression may regain normal perfusion and not appear different from the nearby capillary net on fluorescein angiography.

The pathogenesis of the abnormal retinal reflex produced by a depression in the surface of the retina begins with an occlusion of a fine precapillary arteriole (Fig. 10, top right). If the occlusion produces an area of capillary nonperfusion that persists long enough for ischemic necrosis to form, a depression may evolve. A small infarct in the retina interrupts axoplasmic flow in both directions in the nerve fibers passing through the infarct. The nerve fiber swelling produces cotton-wool spots on the proximal and distal edges of the infarcted area.[7] The infarcted area that leads to a retinal depression is generally small; hence, the cotton wool spots that form on the edges of the infarct may occupy the entire area

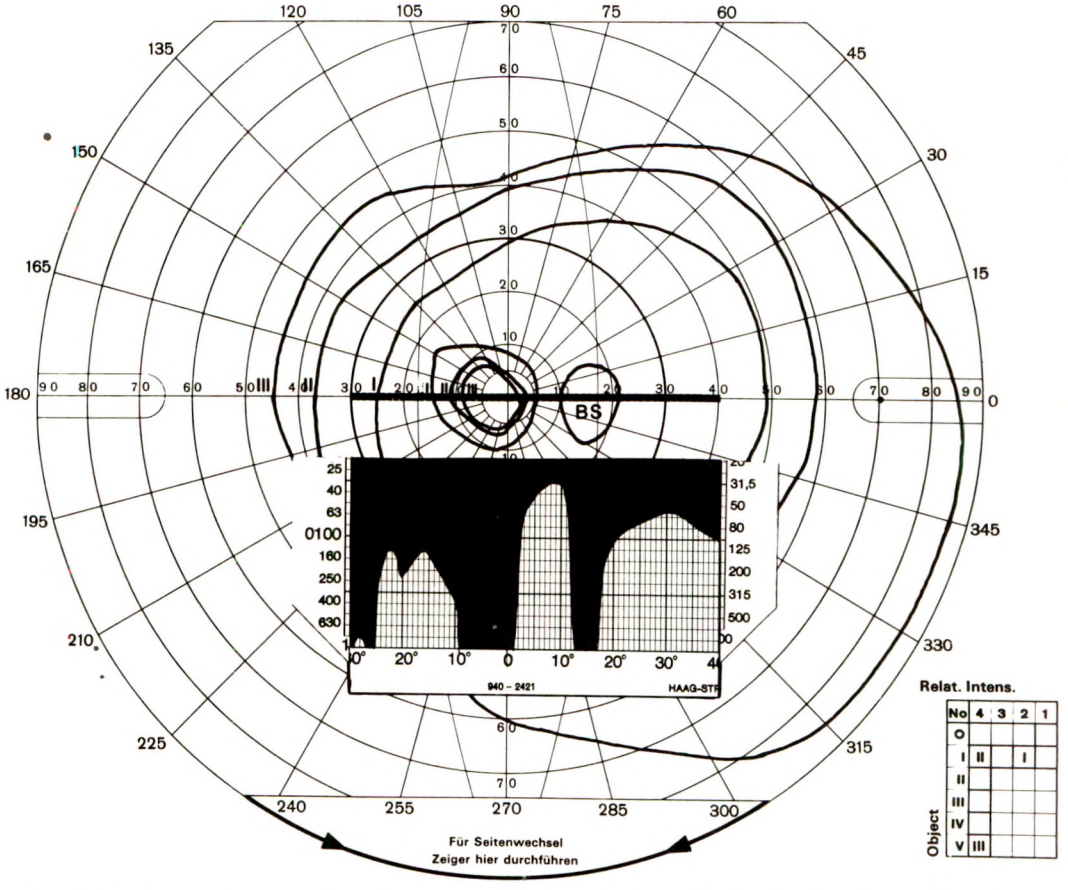


Fig. 8 (Goldbaum) Kinetic and static perimetry. Larger depression involved the fovea. Visual acuity was 6/9 (20/30).

of the infarct. The fluorescein angiogram shows the area of capillary nonperfusion during the acute occlusion (Fig. 10, top right). In most cases, the occluded arteriole reperfuses some time after the ischemic retinal edema or cotton-wool spot forms; some or all of the capillaries reperfuse. As the ischemic retinal edema fades, a depression of the same shape as the ischemic retinal edema may appear. Presumably, the infarcted inner half of the retina necroses, and focal thinning remains. It appears that any disease process that can produce small discrete retinal infarcts and cotton-wool spots can lead to retinal necrosis and depressions.

I have not performed histopathologic examination of any eyes with depressions. However, Foos[8] described a series of gross pathologic specimens with regional thinning of the retina with depressions of the inner surface of the retina after retinal arteriolar occlusion. Some of these patients had arteriosclerosis, diabetes mellitus, rheumatic heart disease, and sickle cell anemia. The histopathologic

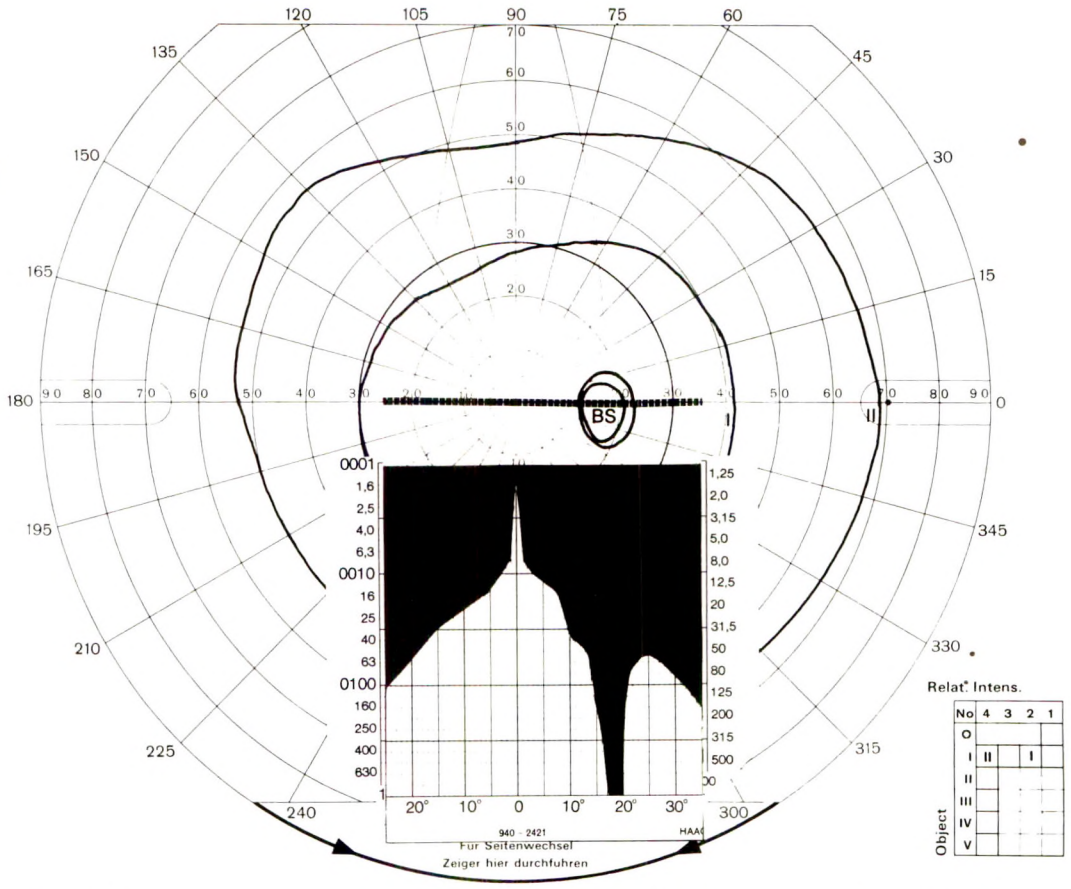


Fig. 9 (Goldbaum) Kinetic and static perimetry of normal eye. Visual acuity was 6/4.5 (20/15) and fixation sensitivity was 1.6 apostilbs.

sections showed necroses of the inner retina and expected sequelae of focal infarction of the retina.

Summary

Retinal depression, a newly observed sign, has been observed as an abnormality in the reflection from the internal limiting lamina produced by depression of the inner surface of the retina after a small retinal infarct. These depressions were first observed in 16 patients with sickling hemoglobinopathies. Additionally, I examined a patient with systemic hypertension, a patient with retinal arteriolitis, and a patient with juvenile onset diabetes mellitus who also had retinal depression.

Acknowledgment

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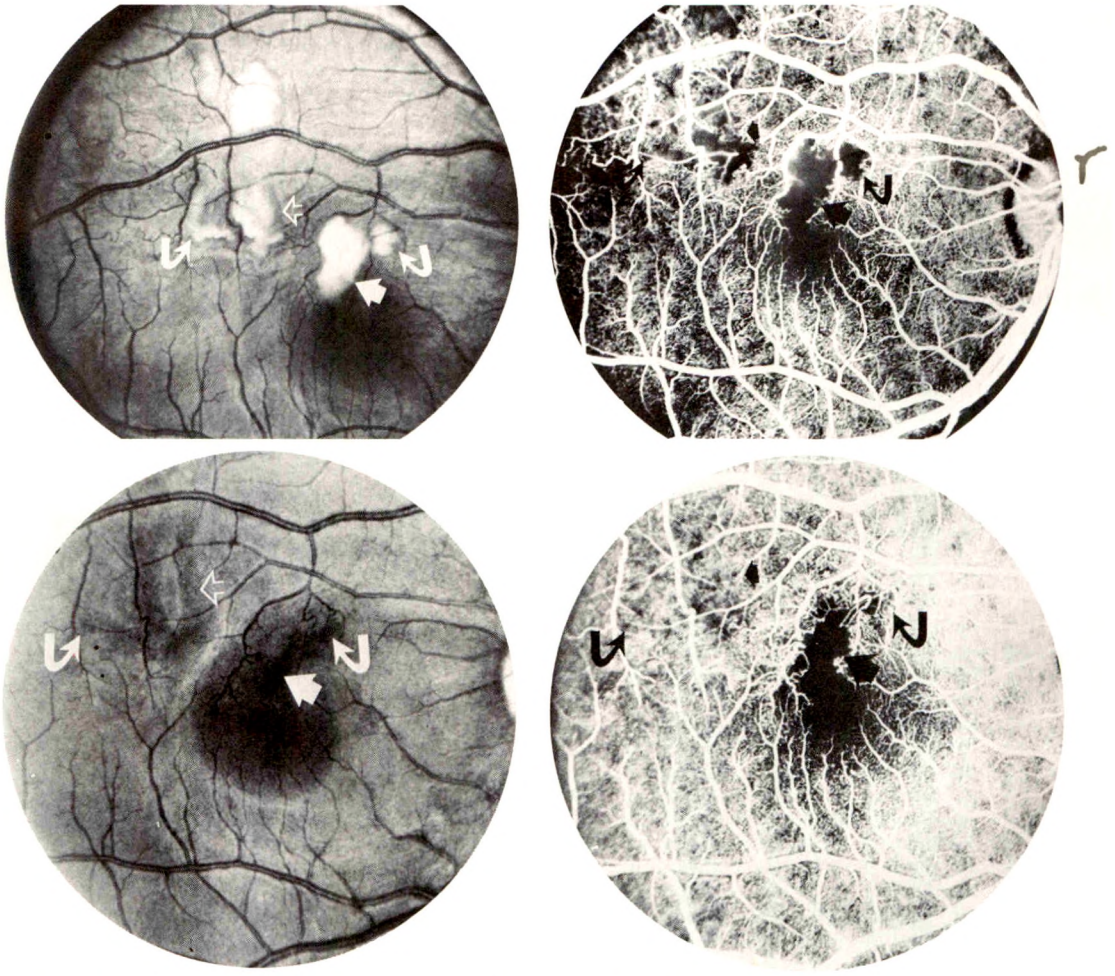


Fig. 10 (Goldbaum). Top left, Several cotton-wool spots which suddenly appeared in a 26-year-old woman being examined daily. Location of arrows corresponds in all parts of the figure. Top right, Corresponding fluorescein angiogram shows areas of retinal capillary nonperfusion at each of cotton-wool sites. Bottom left, Four months after appearance of cotton wool spots, depressions are present at the same locations and with the same shapes as were the cotton-wool spots. Bottom right, Six months after appearance of cotton-wool spots, many of the arterioles and capillaries are reperfusing in the depression sites. The depression superior to the foveal vascular zone is only partially revascularized.

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PIGMENTED MACULAR PUCKER

HORST LAQUA, M.D.
Tübingen, West Germany

Macular pucker occurs spontaneously or as a complication of various ocular diseases. The preretinal membrane is built up by retinal glial cells and collagen. Glial cells are unpigmented, and the preretinal membrane therefore appears translucent or grayish-white depending on the thickness of the membrane.[1–4] The case described in this report of a patient with pigmented macular pucker raises the question of a different cellular origin for the membrane.

CASE REPORT

A 70-year-old woman with a pigmented lesion in the right macula was referred to us for consultation by an ophthalmologist who had known of the condition for four years. The patient's visual acuity had remained stable at 6/30 (20/100) during this time, but recently, she noticed some further deterioration of her vision. Her family history was noncontributory for ocular diseases, although she had a history of a chronic open-angle glaucoma for which she was taking 2% pilocarpine drops three times a day. On initial examination, her visual acuity was R.E.: +1.75 sph 0.05; L.E.: +1.5 sph 0.6. Slit-lamp examination revealed a few pigmented cells (tobacco dust) in the vitreous cavity of the right eye and beginning cataracts in both eyes. The angle was classified as grade 4 in both eyes. Intraocular pressure was R.E.: 10 mm Hg; L.E.: 14 mm Hg.

Ophthalmoscopy of the right eye revealed a grayish-white, Y-shaped preretinal membrane with its center slightly nasal to the foveal area. There was slight elevation of the underlying retina, distortion of the macular vessels, and some traction toward the center of the preretinal membrane with wrinkling of the superficial retinal layers. A large segment of the preretinal membrane was darkly pigmented, hiding the underlying vessels from view (Fig. 1). The posterior vitreous hyaloid face was detached over the whole diseased area. In the fundus periphery at 11 o'clock was a round retinal hole of about 1 disk diameter with pigmentation in its immediate vicinity. The left eye was normal. There was no glaucomatous cupping in either eye.

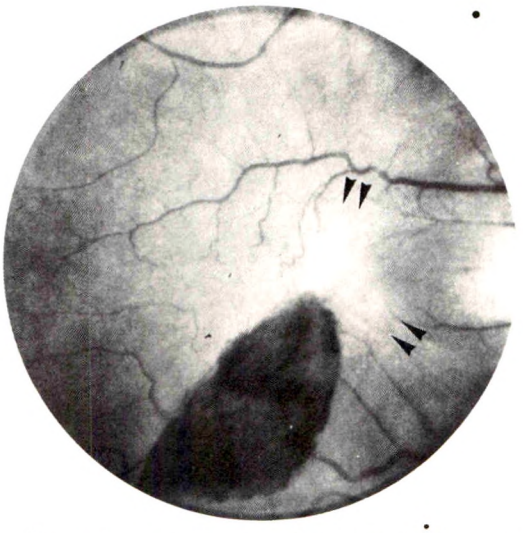


Fig. 1 (Laqua). Pigmented macular pucker. Arrows point to the unpigmented part of the preretinal membrane.

Fluorescein angiography of the right macula revealed blockage of the fluorescence in an area corresponding to the pigmented part of the membrane. There was an obvious distortion of all vessels and diffuse leakage of dye from small capillaries (Fig. 2).

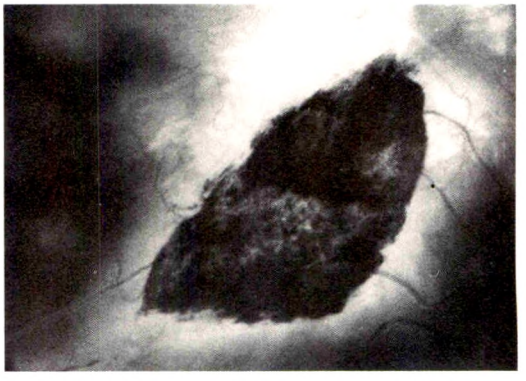


Fig. 2 (Laqua). Late angiogram revealing leakage of dye from retinal capillaries and blockage of fluorescence.

From the Retina Service of the University Eye Clinic, Tübingen, West Germany.

Reprint requests to Horst Laqua, M.D., Schleichstrasse 12, Univ.-Augenklinik, 7400 Tübingen, West Germany.

Discussion

Our case seems to be typical of a long-standing macular pucker in the presence of a peripheral hole. Its plaque-like pigmentation, however, challenges the current concept that the preretinal membrane is built up by glial cells, which are primarily unpigmented.

Pigmented preretinal membranes occasionally occur in eyes with a rhegmatogenous retinal detachment, and recent studies have shown that they arise from retinal pigment epithelial cells. In the presence of a retinal detachment, single retinal pigment epithelial cells liberate themselves from Bruch's membrane, exit through the retinal tear, and settle on the inner retinal surface where they may proliferate and form a membrane.[5,6]

Other studies, however, have shown that preretinal membranes may also arise from unpigmented cells such as glial cells and may become pigmented secondarily because of accumulation of pigmented macrophages and free pigment debris. In these cases, iron pigment instead of melanin is the dominant cause of pigmentation, and a retinal detachment does not necessarily have to be present.[7,8]

The macular pucker in our case may have been of typical glial origin and became pigmented secondarily. To explain the pigmentation in our case, one has to assume that the pigmented macrophage-like cells in the vitreous (tobacco dust), which are constantly found in eyes with a peripheral hole,[9] were incorporated in the preretinal membrane. Another possibility is that cell and pigment debris from a small vitreous hemorrhage occurring at the time of the formation of the peripheral hole were phagocytized and thus caused the pigmentation.

A retinal pigment epithelial origin of the membrane, however, cannot be ruled out. The plaque-like appearance of the pigmented membrane suggests that the pigmentation is caused by a continuous sheet of proliferating pigment-producing cells rather than by secondary pigmentation, which should be more spotty and granular and which should affect the whole membrane evenly. The access for the retinal pigment epithelial cells to proliferate onto the inner retinal surface could be provided by the peripheral hole which, in our case, showed clinical evidence of proliferative activity in its immediate vicinity. Strikingly similar plaque-like membranes studied histopathologically in the owl monkey were composed of retinal pigment epithelial cells.[10] Although both theories offer an acceptable explanation, histologic studies are necessary to establish the cellular origin of pigmented macular pucker.

Summary

A 66-year-old woman developed a darkly pigmented preretinal membrane. In the fundus periphery there was a round retinal hole about one disk diameter with pigmentation in its immediate vicinity. Pigmented, preretinal membranes arise from retinal pigment epithelium cells that exit through a retinal tear and settle on the inner retinal surface where they proliferate and form a membrane. Some preretinal membranes arise from unpigmented cells such as glial cells and become colored with iron pigment because of the accumulation of pigmented macrophages and free pigment debris. A retinal hole is not necessary for the occurrence of a glial membrane.

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OPHTHALMIC MINIATURE

Binocular Ophthalmoscope—We owe to Dr. Giraud-Teulon, and following him, Mr. J. Z. Lawrence, our thanks for the invention of the binocular ophthalmoscope, by means of which we are enabled to save a great deal of time and uncertainty in determining the position of extravasations, exudations, deposits, etc., in the vitreous humor, retina and choroid. It is true, as Dr. Schweigger admits, that with the monocular ophthalmoscope it is possible to ascertain nearly all that the binocular instrument can reveal to us; but a moment's glance with both eyes is worth an hour's gaze with one. Probably in a short time ophthalmologists will use it to the exclusion of the monocular ophthalmoscope. A comparison of the two would be better than any description we can here give. Time will undoubtedly simplify as well as cheapen this instrument. It is, in the highest sense of the term, an advance upon our previous means of observation. Simply as a scientific or philosophical instrument, it will be of great value, as probably enabling us to settle many points in reference to binocular vision and so-called stereoscopic effect. It is a new means of experimenting in this field of physiological optics. Its general use will be looked forward to with interest by both the philosophical and pathological ophthalmologist.

Trans. Am. Ophthalmol. Soc. 3:5, 1866

PREVENTION OF VITREOUS LOSS IN APHAKIC KERATOPLASTY

STEVEN L. LEMPERT, M.D., MARK S. JENKINS, M.D., AND STUART I. BROWN, M.D.
Pittsburgh, Pennsylvania

Before the 1960s, penetrating keratoplasties in aphakic eyes had almost uniformly poor results.[1,2] Some of the reported reasons for the aphakic graft failures were complications associated with the vitreous, that is, vitreous dislodging the corneal graft during surgery,[3] vitreous corneal contact, and postoperative glaucoma.[4]

The necessity of preventing vitreous corneal contact in corneal transplantation has stimulated various preventative techniques. Filatov[3] inserted a spatula across the anterior chamber to hold the vitreous back before trephining the cornea. Casey[5] placed an intraocular lens in a separate operative procedure before grafting in aphakic cases. Fine[6] used vitreous aspiration through the pars plana to prevent vitreous prolapse. Maumenee[7] suggested liquid vitreous aspiration through the pupil after the host cornea was excised. Sanders[8] recommended an anterior vitrectomy with cellulose sponges, which was commonly used until vitreous cutting devices were introduced. Although anterior vitrectomy is probably important in achieving a transparent corneal graft in aphakic eyes, recent evidence indicates that it is also associated with increased incidences of retinal detachment,[9] macular edema,[10] and glaucoma.[11]

We report herein a simple method of gradual decompression of the anterior chamber to prevent vitreous loss in aphakic corneal transplantation.

From the Department of Ophthalmology, University of Pittsburgh School of Medicine and Eye and Ear Hospital, Pittsburgh, Pennsylvania.

Reprint requests to Stuart I. Brown, M.D., Department of Ophthalmology, Eye and Ear Hospital, 230 Lothrop Street, Pittsburgh, PA 15213.

MATERIAL AND METHODS

We studied 11 patients with aphakic bullous keratopathy and either an intact vitreous face or loose vitreous behind the iris plane.

The operating microscope, O'Brien akinesia, and retrobulbar anesthesia were used in all keratoplasties. After placement of a wire eyelid speculum, a Flieringa ring was attached to the episclera by using four interrupted 7-0 silk sutures. A 7.5-mm trephine was used to excise the donor corneal button, which was placed in a moist chamber, and to make a 0.3- to 0.4-mm incision in the recipient cornea. In the first six cases, a 2-mm incision into the anterior chamber was made within the trephine incision with a Ziegler knife. The wound was spread to allow the aqueous to exude slowly until the eye was soft. The technique was simplified and shortened in the last five cases. A 25-gauge needle on a 1-ml tuberculin syringe was passed through the trephine incision into the anterior chamber. Approximately 0.2 to 0.5 ml of aqueous was slowly withdrawn from the anterior chamber. The anterior chamber was then entered through the trephine incision with either a razor blade or Zeigler knife, and the host corneal button was removed with corneal scissors. We carefully avoided putting any pressure on the globe with the eyelid speculum or during surgical manipulation. The corneal graft was quickly sutured to the host, first with eight interrupted 9-0 nylon sutures, followed by either a 10-0 nylon or 10-0 Prolene continuous suture.

RESULTS

The vitreous face remained intact in eight of the 11 procedures (Figs. 1 and 2).

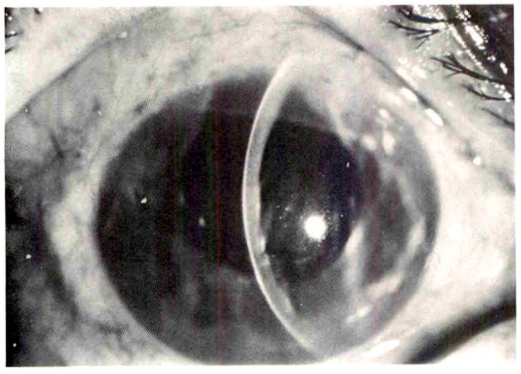


Fig. 1 (Lempert, Jenkins, and Brown). Preoperative appearance of eye with aphakic bullous keratopathy and keyhole pupil.

Vitreous was lost in three cases, but not with a gush or progressive effusion from the wound. All grafts have remained transparent from six to 26 months postoperatively, and we have not seen vitreous contact with the graft endothelium.

Discussion

In 19 consecutive corneal transplantations on aphakic eyes with intact vitreous faces before the development of this method, we were able to maintain an intact vitreous face in only two of the eyes.

In addition to reducing the intraocular pressure, the technique appears to avoid the sudden gush of aqueous followed by vitreous, which occurs on opening these eyes. Theoretically, the technique could also be useful in secondary implantation of intraocular lenses.

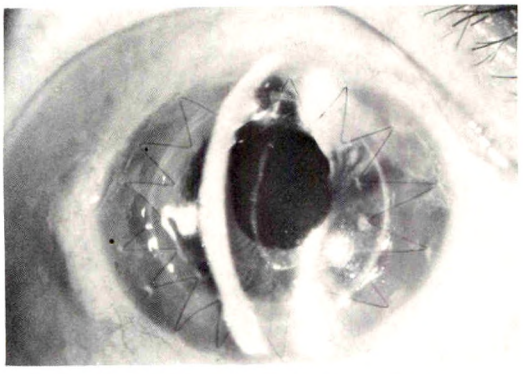


Fig. 2 (Lempert, Jenkins, and Brown). Postoperative appearance of eye in Figure 1. Corneal graft is transparent and vitreous face is intact.

Although the series was too small for any definitive conclusions, none of the eight eyes with intact vitreous faces developed retinal detachment or gross macular edema or required carbonic anhydrase inhibitors postoperatively. Only two of the eight patients had postoperative increases in intraocular pressure, which were controlled with pilocarpine.

Summary

Controlled aspiration of aqueous before excising the recipient cornea resulted in maintenance of an intact vitreous face during aphakic penetrating corneal transplants in eight of 11 eyes. Vitreous corneal contact or subsequent graft opacification has not occurred in the study group during the observation period.

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OCULAR PERFORATION FOLLOWING RETROBULBAR ANESTHESIA FOR RETINAL DETACHMENT SURGERY

ROBERT C. RAMSAY, M.D., AND WILLIAM H. KNOBLOCH, M.D.
Minneapolis, Minnesota

One of the more unusual intraoperative complications of retinal detachment surgery is perforation of the globe by the retrobulbar needle during the injection of a local anesthetic agent. Retinal surgery requires the use of both regional and general anesthetic methods. At the University of Minnesota, approximately 85% of retinal reattachment procedures are done with regional anesthesia. General anesthesia is generally reserved for complicated reoperations, detachments with breaks in the posterior pole, and patients under the age of 20 years and those who have recently undergone anterior segment surgery.

The advantages of regional anesthesia include a more efficient use of operating room time and a lower incidence of cardiopulmonary complications and postoperative nausea and vomiting.[1,2] The major disadvantage of retinal surgery is the limited duration of action. However, episcleral buckling techniques have shortened operating time, which permits the use of regional anesthesia in the majority of cases. Local complications of retrobulbar anesthesia include orbital hemorrhage, central retinal artery occlusion, and optic neuropathy and atrophy.[3–6] Intravascular injection of an anesthetic agent may produce systemic toxicity.[7]

Cibis[7] reported one case of perforation of the globe by the injection needle in a series of 1,000 patients who underwent retinal surgery with local anesthesia. Perforation of the globe during intraocular injection of the anesthetic agent has also occurred in highly myopic eyes with posterior staphylomas.[4]

We report herein three examples of perforation of the globe by the injection needle in a series of 4,000 patients who underwent retinal surgery with local anesthesia. In each case 2% lidocaine with epinephrine and hyaluronidase was injected with a 25-gauge 35-mm nondisposable needle.

CASE REPORTS

Case 1—A 21-year-old woman came to our office with a retinal detachment in the left eye after blunt trauma. This eye was amblyopic secondary to anisometropia with a refractive error of −19.50 diopters. The best corrected visual acuity was 6/120 (20/400). Preoperative examination disclosed a temporal retinal detachment involving the macula with multiple breaks from 2 to 3 o'clock at the equator (Fig. 1).

A single retrobulbar injection was given during surgery without any noticeable problem. We noted marked hypotony of the globe when preparing the conjunctival incision. Examination of the fundus showed that the needle had entered the eye inferotemporally posterior to the equator, perforated the detached retina, passed through the vitreous cavity,

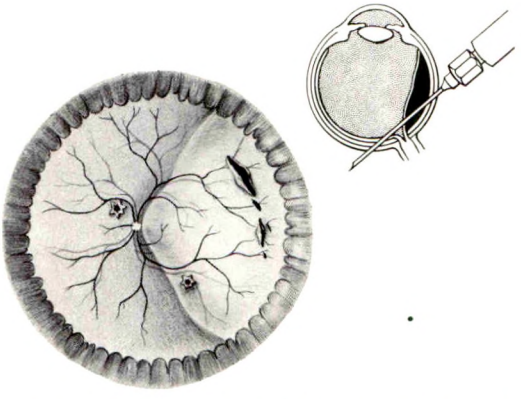


Fig. 1 (Ramsay and Knobloch). Case 1. Double perforation of the globe by the retrobulbar needle with passage through both detached and attached retina.

From the Retina Service, Department of Ophthalmology, University of Minnesota, Minneapolis, Minnesota. This study was presented in part at the Annual Meeting of the Retina Society, Los Angeles, California, Nov. 5, 1977.

Reprint requests to Robert C. Ramsay, M.D., Box 493 Mayo Building, Department of Ophthalmology, University of Minnesota, Minneapolis, MN 55455.

went out superior-nasal to the optic nerve, and perforated the attached retina. Lidocaine was injected outside the globe in the superior-nasal quadrant. An encircling buckling procedure closed the previously existing tears. Transscleral cryopexy was applied to both perforation sites, and a 5-mm episcleral sponge was placed under the perforation site through the detached retina only. The globe was reconstituted by injecting air into the vitreous cavity through the pars plana.

The retina was reattached postoperatively. The best corrected visual acuity was 6/120 (20/400). Figure 2 shows the healed perforation site above the optic nerve with localized epiretinal membranes. The membranes have remained stable during the 15-month follow-up period.

Case 2—A 52-year-old woman had a myopic refractive error of −9.00 diopters. A retinal detachment in the left eye had been successfully repaired. The right eye underwent cataract surgery and two months later developed a retinal detachment. The preoperative examination showed a temporal detachment involving the macula with aphakic horseshoe breaks in the 8 and 11 o'clock meridians and visual acuity reduced to 6/60 (20/200) (Fig. 3).

During surgery, the needle encountered increased resistance in the orbit. The needle was withdrawn and reinserted, and the injection was completed. Hypotony was noted on opening the conjunctiva, and blood was found in the subretinal space. When pressure was applied to the eye, subretinal fluid and blood drained from a perforation site inferior and temporal to the macula and approximately 8 mm posterior to the equator. The retina was not perforated. No repair of the perforation site was attempted,

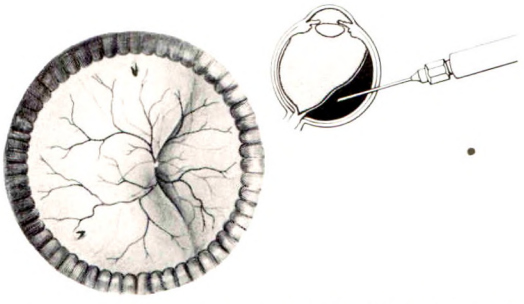


Fig. 3 (Ramsay and Knobloch). Case 2. Single perforation of the globe by the retrobulbar needle into the subretinal space without injury to the detached retina.

and an encircling buckling procedure closed the pre-existing breaks. Postoperatively the subretinal hemorrhage cleared slowly without further problems (Fig. 4). The eye reached a visual acuity of 6/6 (20/20), and no additional complications have been noted during the seven-month follow-up period.

Case 3—A 58-year-old man came to our office with a recurrent retinal detachment in the right eye. The refractive error of the eye was −9.00 diopters, and preoperative visual acuity was 6/6 (20/20). Examination revealed a quadrantic detachment with a tear located in the 10 o'clock meridian along the posterior edge of the previous buckle (Fig. 5). Because of initial resistance to the retrobulbar needle, the needle was withdrawn and reinserted before completion of the injection. Hypotony was not noted on

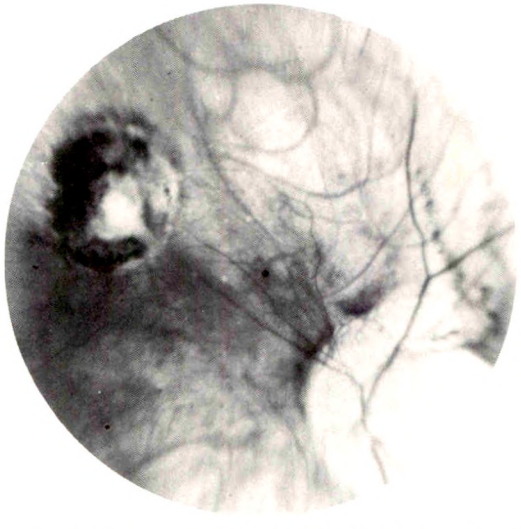


Fig. 2 (Ramsay and Knobloch). Case 1. Localized epiretinal membrane formation at the site of the healed perforation site above the optic nerve.



Fig. 4 (Ramsay and Knobloch). Case 2. Residual subretinal blood and the perforation site three months after surgery.

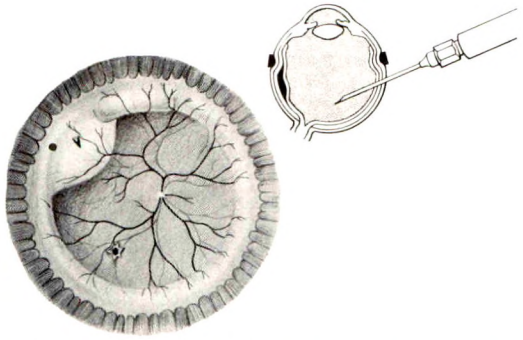


Fig. 5 (Ramsay and Knobloch). Case 3. Single perforation of the globe by the retrobulbar needle through attached retina.

opening the conjunctiva. During examination of the interior of the eye, blood appeared in the vitreous cavity after having come from a perforation site through the attached retina posterior to the old encircling band in the inferotemporal quadrant. During surgery, the perforation site was not treated, and the detachment was repaired by repositioning the previous buckle to close the new break. Immediately after surgery xenon arc photocoagulation was applied to the perforation site. Postoperatively, the retina reattached and the vitreous hemorrhage slowly cleared. The best corrected visual acuity was 6/6 (20/20), and no further complications have been noted in the 24-month follow-up period.

Discussion

Of 4,000 patients who had retinal detachments and who had undergone surgery with local anesthesia, there were three examples of perforation of the globe by the retrobulbar needle. This incidence is similar to that reported by Cibis.[7] A major contributing factor in all cases was the presence of significant myopia. Myopic eyes are more susceptible to perforation because of their increased anteroposterior diameter and thinner sclera as compared to emmetropic or hyperopic eyes. Posterior staphyloma increases the risk, although this defect did not occur in any of our cases. Injection with a rounded needle, as recommended by Atkinson,[8] should reduce the incidence of this complication.

Each of our cases presented a different clinical problem. In the first case, the retrobulbar needle perforated both detached and attached retina. The site of perforation through the detached retina was treated in the same way as a primary retinal break, that is, with cryopexy and external tamponade. The perforation site in the attached retina was treated with cryopexy alone.

In the second case, the needle perforated the sclera and choroid to enter the subretinal space, but did not injure the retina. The perforation site was small and self-sealing and therefore, was not repaired.

In the third case, the perforation site was also through the attached retina, which produced a vitreous hemorrhage. We chose to treat the break with photocoagulation immediately postoperatively, instead of with cryopexy during surgery, simply to avoid dissection of the involved quadrant in a previously operated eye.

The successful anatomic results obtained in all three cases were influenced by the lack of a severe postoperative inflammatory reaction with subsequent intraocular cellular proliferation. The inadvertant injection of corticosteroids into the vitreous elicits a marked inflammatory response and often causes loss of vision.[9] Lidocaine would induce a similar response, although experimentally, the drug is not retinotoxic.[10] Fortunately, the drug was injected outside the globe in all three of our cases. Although epiretinal and vitreous membranes were noted near the perforation site through the attached retina in the first case, they have not progressed during the 15 months of follow-up. Experimentally and clinically, intraocular cellular proliferation with vitreous membrane formation has occurred at the site of the planned injections into the vitreous during retinal surgery.[11–13] Similar proliferations may also occur after occult perforation of the globe during strabismus surgery.[14–16]

Whereas local anesthesia remains use-

ful for most retinal reattachment procedures, general anesthesia should be considered in highly myopic eyes to avoid the complication of perforation of the globe by the retrobulbar needle.

SUMMARY

We encountered three examples of the perforation of the globe by the retrobulbar needle in a series of 4,000 patients who had undergone retinal reattachment surgery with local anesthesia. The presence of significant myopia was a contributing factor in all three cases. We managed the perforation site through the detached retina with cryopexy and external tamponade, and we treated perforations through the attached retinas either with cryopexy at surgery or photocoagulation postoperatively.

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PERIPAPILLARY PIGMENTARY RETINAL DEGENERATION

KENNETH G. NOBLE, M.D., AND RONALD E. CARR, M.D.
New York, New York

The posterior pole of the retina is involved in a number of degenerative and inflammatory conditions. If the macula is spared and vision remains normal, these diseases may be asymptomatic and escape detection.

Over the past several years, we have studied four asymptomatic patients who demonstrated widespread peripapillary degeneration.

This disorder is characterized by a bilateral, usually symmetrical transparency of the pigment epithelium associated with bone spicule pigment clumping in a peripapillary distribution with extension nasal to the disk and temporally in an arcuate fashion.

Follow-up examination in three cases revealed no progression of the pigmentary changes, and this localized pigmentary dystrophy appears to have a benign process.

METHODS

All patients underwent ophthalmological examination including perimetry, fluorescein angiography, retinal profiles, electroretinography, and electro-oculography. The procedures followed for such testing have been outlined in previous reports.[1,2]

From the Department of Ophthalmology, New York University Medical Center, New York, New York. This work was supported in part by grant EY00213 from the National Eye Institute, National Institutes of Health.

Reprint requests to Kenneth G. Noble, M.D., Department of Ophthalmology, New York University School of Medicine, 550 First Ave., New York, NY 10016.

RESULTS

All patients were in excellent general health; they were referred to us because of fundus changes and none of them had complaints. After we questioned them more carefully, three acknowledged some difficulty with side vision and night vision, but this did not interfere with their life styles. Visual acuity was 6/6 (20/20) in both eyes for Cases 3 and 4; 6/7.5 (20/25) in both eyes for Case 1; and R.E.: 6/6 (20/20), L.E.: 6/7.5 (20/25) for Case 2 (Table). The scotoma corresponded well to the ophthalmoscopic and fluorescein angiographic areas of disease.

The final retinal threshold sensitivities were measured after 30 minutes of dark adaptation at various loci, ranging from the fovea to 30 degrees nasal, and 30 degrees temporal retina. The threshold sensitivity was elevated in the ophthalmoscopically affected retina and was normal in normal appearing retina.

In all cases, electroretinograms revealed only a slight reduction of the scotopic b-wave amplitude, which corresponded with the amount of retina damaged. The photopic response was normal. Photopic and scotopic latencies were also normal.

The electro-oculographic light rise was normal in the patient who had the most extensive involvement (Case 1).

The major ophthalmoscopic finding was a metallic, grayish sheen radiating from the disk along the inferior and superior vessels to a variable extent (Figs. 1 and 2). In both eyes in Case 1 and the left eyes in Cases 2 and 3, the inferior and superior extensions joined temporal to the

TABLE

FINDINGS IN PATIENTS WITH PERIPAPILLARY PIGMENTARY RETINOPATHY

Case No.	Age Race, Sex	Presenting Symptom	Vision	Retinal Profiles	Visual Field (Goldmann Perimeter 1/4 mm² White)	ERG (Scoptopic B-wave)	Ophthalmoscopic Findings	Follow-up (yrs)
1	45 W, M	None	Both eyes: 6/7.5 (20/25+)	L.E.: elevated superiorly, nasally, and temporally from 3 to 25 degrees, normal at 30 degrees	Bilateral ring scotomata-nasally 3 to 25 degrees, temporally 5 to 40 degrees	Slight reduction (EOG) 250% both eyes	Bilateral symmetrical annular ring with a tapetal reflex surrounding the central retina. Bone spicule pigmentation present but mild	1
2	50 W, M	None	R.E.: 6/6 (20/20) L.E.: 6/7.5 (20/25)	R.E.: elevated temporally and nasally from 10 to 20 degrees	Inconsistent responses	Slight reduction	R.E.: Peripapillary sheen extending along infero-temporal vessels. L.E.: Annular ring of tapetal reflex with heavy pigment proliferation nasal to disk	1
3	31 W, M	None	Both eyes: 6/6 (20/20)	R.E.: elevated from 10 to 30 degrees temporally	R.E.: Inferior and superior arcuate scotoma L.E.: Ring scotoma with 5 degree central vision	Normal	R.E.: Peripapillary sheen and transparency extending along inferior and superior temporal vessel arcades L.E.: Perimacula annular ring of pigmentary sheen	—
4	39 B, F	None	Both eyes: 6/6 (20/20)	R.E.: elevated 20 to 30 degrees nasally and temporally		Slight reduction	R.E.: Peripapillary sheen with projections into all quadrants L.E.: Peripapillary sheen with small superior extension	2

macula forming an annulus. Interspersed within the affected retina were bone spicule pigment clumping and areas of pigment epithelial transparency. Although the margins were not sharply delineated, the border where diseased retina ended and normal peripheral retina began was apparent. In all cases the retinal vessels, optic disk, macula, and periphery appeared normal.

The retinal involvement was bilateral and either symmetric (Cases 1 and 3), or only moderately asymmetric (Cases 2 and 4) in its appearance.

The major finding on fluorescein angiography was a hyperfluorescence of dye caused by a pigmentary transmission defect (Figs. 3-9). The area of hyperfluorescence corresponded identically to the areas of pigmentary change and was a better indicator of the exact borders of the lesions. The pigment accumulation resulted in the expected hypofluorescence. More peripheral areas were normal. A ring of perifoveal atrophy in Case 1 showed hyperfluorescence.

There was no history indicative of hereditary ocular disease (such as consan-

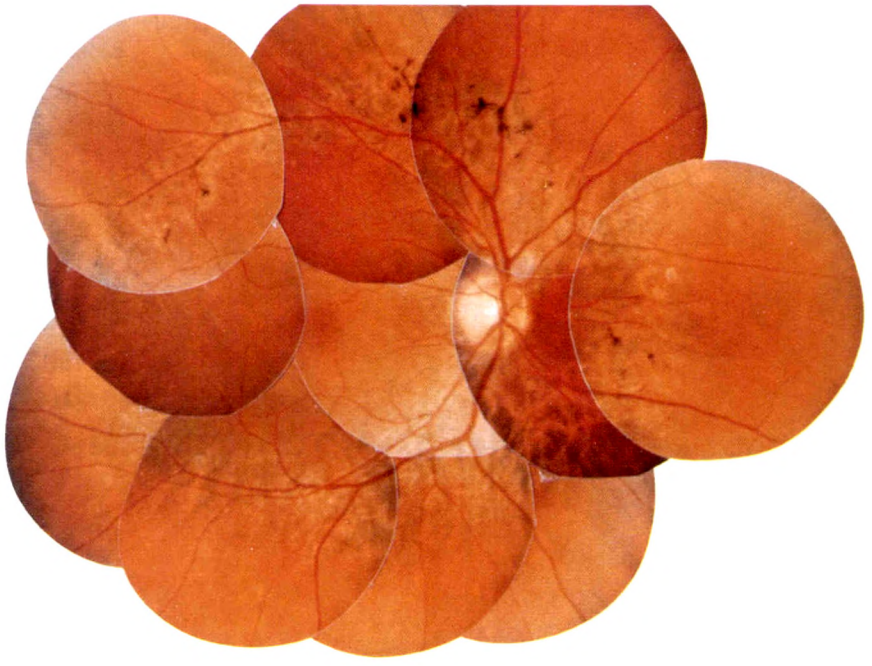


Fig. 1 (Noble and Carr). Case 1. The posterior pole of the right eye shows the symmetrical distribution of a pigmentary tapetal reflex extending from the disk along the inferior and superior vessel arcades and joining temporal to the macula. Occasional bone spicule pigmentation may be seen in the affected retina. The optic disk and retinal vessels are normal.

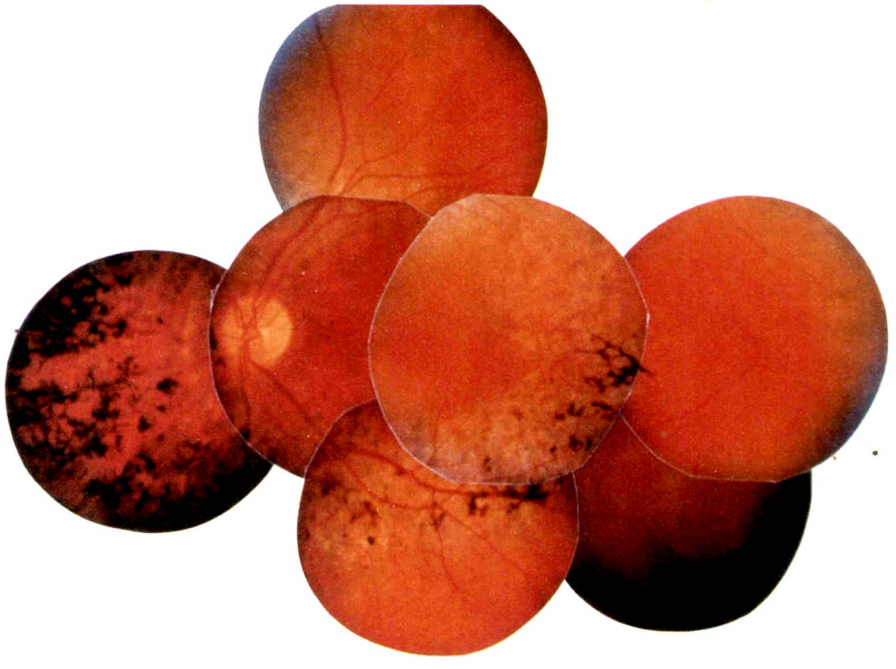


Fig. 2 (Noble and Carr). Case 2. The left eye has an annular distribution of the pigmentary sheen reflex with a heavy accumulation of pigment nasal to the disk.

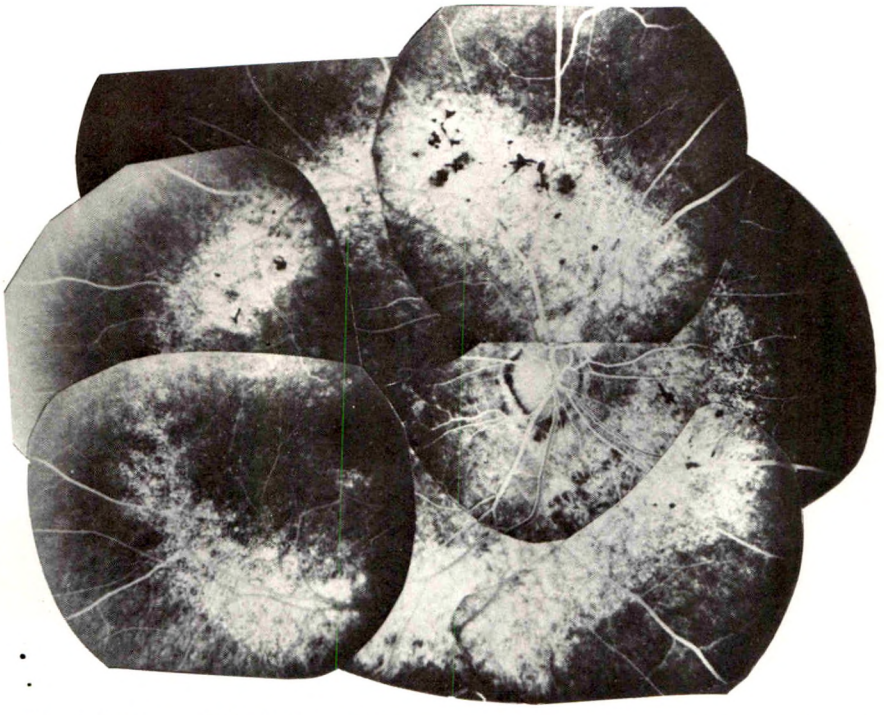


Fig. 3 (Noble and Carr). Case 1. Fluorescein angiography in the right eye shows hyperfluorescence in the affected retinal tissue.

guinity or similarly affected relatives), although only the sister of one patient (Case 1) was examined.

We saw two patients (Cases 1 and 2) after one year, and one (Case 4) after a two-year interval. In no instance was there evidence of progression of the lesions or a decrease in visual acuity. One patient (Case 3) was lost to follow-up.

Discussion

Peripapillary or pericentral pigmentary retinopathy is an asymptomatic disorder that appears to have a benign prognosis.

The primary disease process involves the retinal pigment epithelium-photoreceptor complex in a peripapillary distribution with extension nasal to the disk and temporally in an arcuate distribution. This is a localized or geographic degeneration as evidenced by visual field scotoma corresponding to the distribution of the retinal lesion; decreased retinal sensitivity in abnormal retina and normal sensitivity in ophthalmoscopically unaffected areas; slight reduction in the electroretinogram with normal latencies; normal electro-oculographic light rise; and pigment transmission defect with hyperfluorescence in affected retina and normal fluorescence in adjacent retina.

All the referring physicians in our study wished to rule out the diagnosis of a generalized tapetoretinal degeneration, presumably because of the bone spicule formation and the pigmentary tapetal sheen. Additionally, three patients admitted to some difficulty with peripheral and night vision. But the normal caliber of arterioles even in the involved retina, the

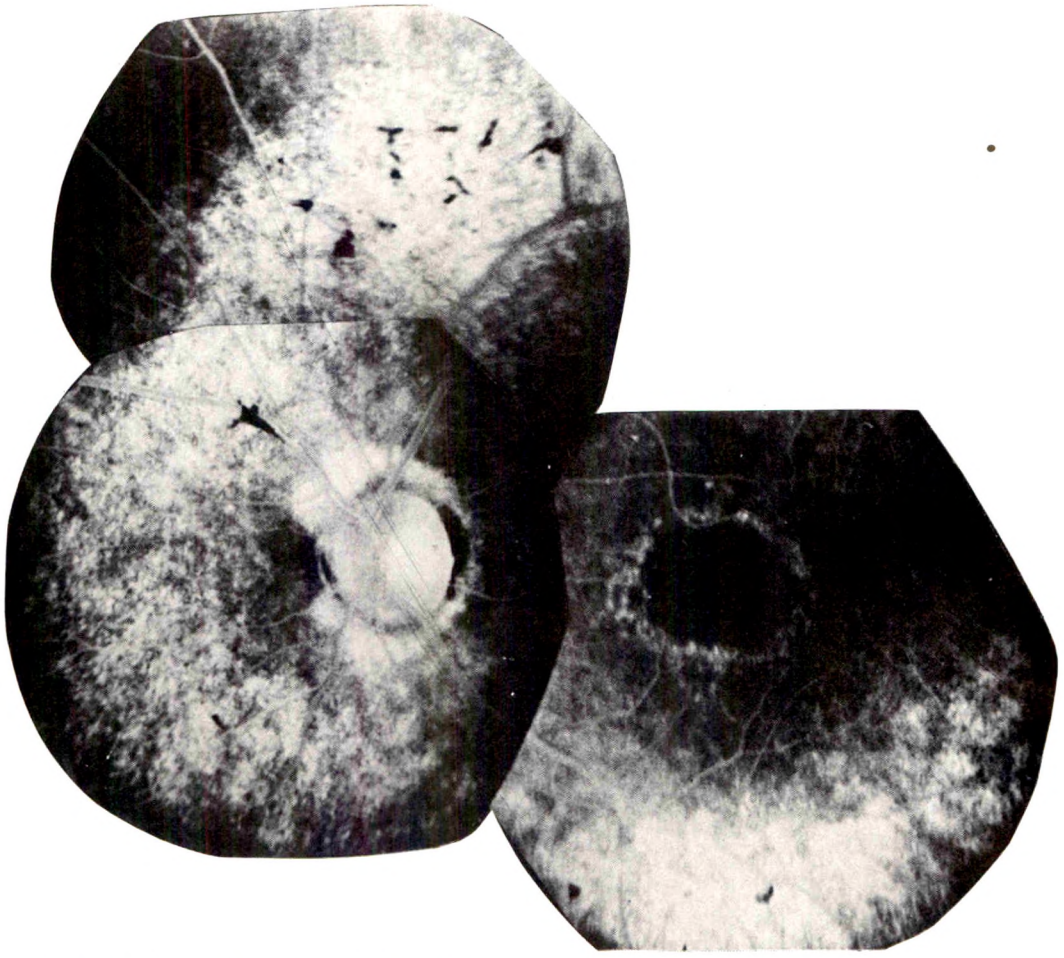


Fig. 4 (Noble and Carr). Case 1. Hyperfluorescence in the affected retinal tissue of the left eye. A perifoveal ring of hyperfluorescence indicates pigment disturbances in this area.

normal retinal sensitivity in uninvolved retina, the essentially normal electroretinogram with normal latencies, and the normal electro-oculographic light rise are all inconsistent with tapetoretinal dystrophy.

The terms sector retinitis pigmentosa, central retinitis pigmentosa, and pericentral retinitis pigmentosa have been used to describe disorders that are segmental in nature, but in which the affected retinal area resembles retinitis pigmentosa. Duke-Elder[3] defined central pigmentary dystrophy as a pigmentary disturbance [which] takes the form of an island round the macula," whereas pericentral pigmentary dystrophy shows a " . . . picture between the true central and classical equatorial lesions, wherein a pigmented zone occurs immediately around the macula, often leaving good central vision." These entities have been reported in families; sector retinitis pigmentosa is usually inherited as an autosomal dominant disorder[4] and central and pericentral retinitis pigmentosa as autosomal recessive disorders.[5]

Sector retinitis pigmentosa (usually in-

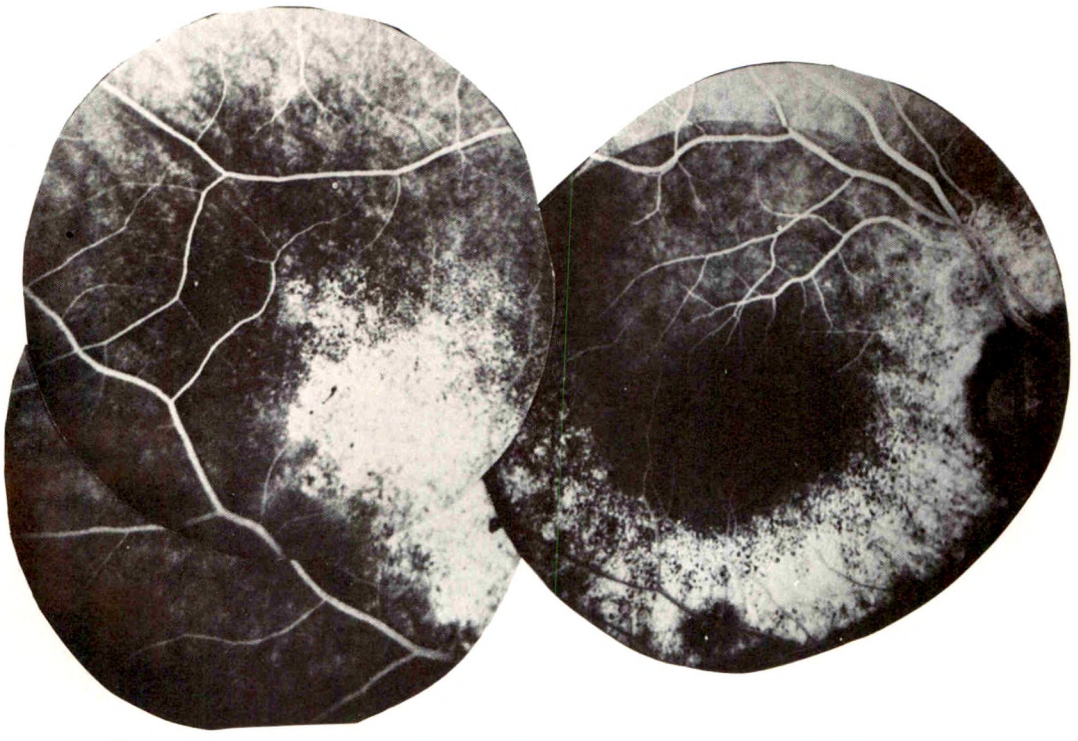


Fig. 5 (Noble and Carr). Case 2. Fluorescein angiography of the right eye shows hyperfluorescence in the ophthalmoscopically affected areas. Peripheral areas of retina show a normal fluorescein pattern.



Fig. 6 (Noble and Carr). Case 2. Hyperfluorescence in the ophthalmoscopically affected area of the left eye.

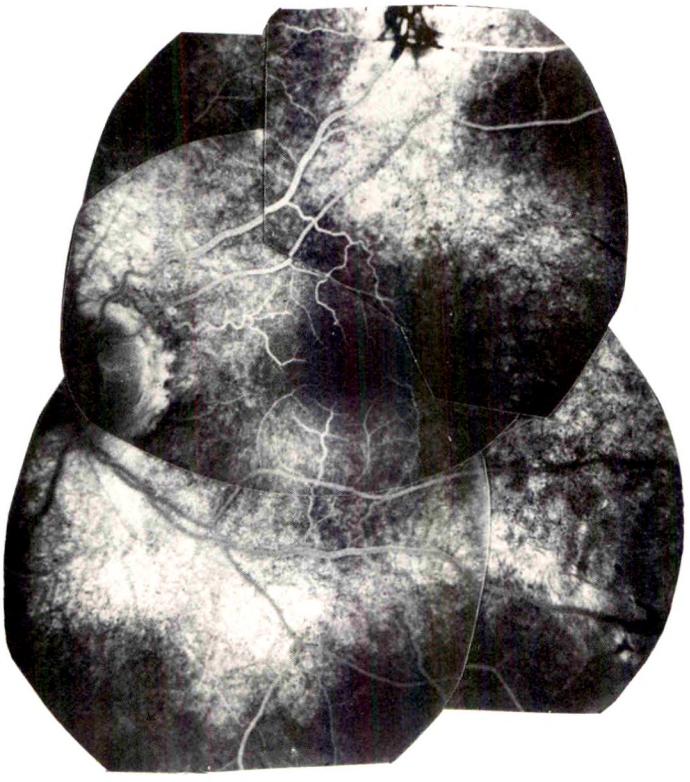


Fig. 7 (Noble and Carr). Case 3. Fluorescein angiogram of left eye shows an annular ring of hyperfluorescence surrounding a normal macula.

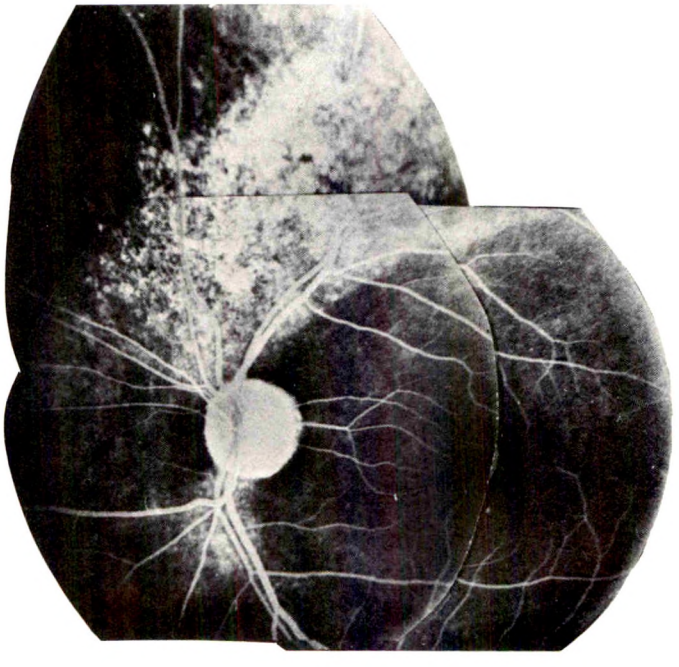


Fig. 8 (Noble and Carr). Case 4. Fluorescein angiograms show the nasal extension in the right eye, as well as along the temporal vessels.

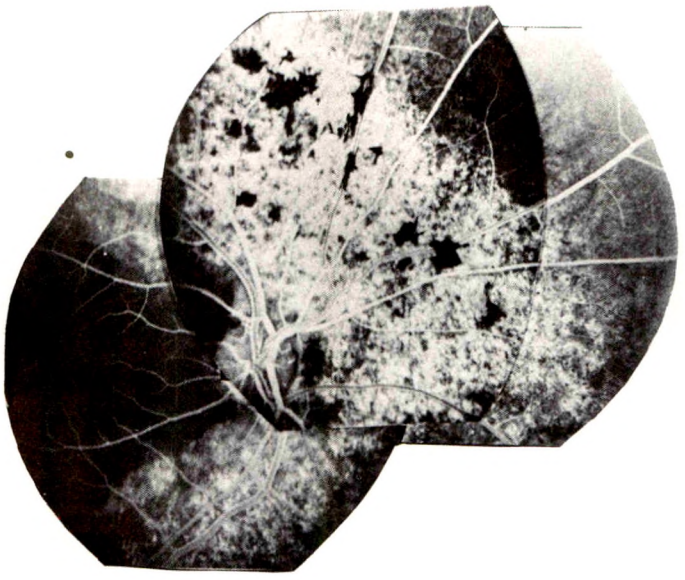


Fig. 9 (Noble and Carr). Case 4. The left eye has only a small superior extension from the disk.

volving an inferior retinal quadrant), central retinitis pigmentosa (involving the macula), and our cases of peripapillary pigmentary retinal degeneration may all represent a similar pathologic process, but each has a different geographic presentation. These three disorders all share the same characteristics: localized pigmentary changes, including bone spicule formation; minimal progression into normal retina; angiographic evidence of a pigmentary transmission defect with hyperfluorescence and without choriocapillaris atrophy; and visual function tests that reflect a local process and not a generalized dysfunction.

The generalized tapetoretinal degeneration known as retinitis pigmentosa always reveals a diffuse dysfunction of the photoreceptors. The ophthalmoscopic picture may mimic a localized disorder since pigmentary changes may be confined to the central retina, the peripapillary region, or a particular segment of the retina. However, electrophysiologic and psychophysical tests indicate widespread dysfunction of the photoreceptors.

Peripapillary pigmentary retinopathy must also be differentiated from peripapillary choroidal sclerosis, a disease affecting the same region. The term peripapillary choroidal sclerosis includes a variety of disorders such as helicoid degeneration,[6] serpiginous choroidopathy,[7] geographic choroidopathy,[8–10] and circinate choroidal sclerosis.[11] Maumenee[10] suggested that these disorders may cover a wide spectrum of diseases ranging from choroidal inflammation to choroidal vascular abiotrophy. Common to all the disorders within this framework is atrophy of the choriocapillaris.

Whereas ophthalmoscopic pictures of pigmentary and choriocapillaris dystrophy may look similar, especially in the early stages of the disease, fluorescein angiography differentiates them.[12] Primary choriocapillaris pathology will show an absence of the choriocapillaris flush, and the larger choroidal vessels will be visible (Fig. 10). In disease confined to the pigment epithelium, the choroidal vessels may be easily seen initially in the choroidal phase, (Fig. 11, left) but by the arterial or early venous phase, the normal choriocapillaris flush is seen as hyperflu-



Fig. 10 (Noble and Carr). Fluorescein angiogram shows peripapillary atrophy of the choriocapillaris and the large choroidal vessels are visible.

orescence (Fig. 11, right). In none of these four cases was there evidence on fluorescein angiography of choriocapillaris atrophy.

Finally, pigmented paravenous chorioretinal degeneration [6] can have a similar appearance. The ophthalmoscopic hallmark of this disease is a paravenous accumulation of pigment that may be associated with chorioretinal atrophy. Although most of the changes in our patients followed the temporal vessel ar-



Fig. 11 (Noble and Carr). Case 3. Left, In the choroidal phase the large choroidal vessels are easily seen through the pigment transmission defect. Right, By the late arterial phase the choriocapillaris vessels have filled and leaked fluorescein, obscuring the larger choroidal vessels.

cades, there were many involved areas unrelated to the distribution of the retinal vasculature.

Summary

We studied four patients with peripapillary pigmentary retinal degeneration, an asymptomatic disorder that was probably benign and nonprogressive.

The ophthalmoscopic appearance showed a segmental, grayish metallic sheen in association with bone spicule pigmentation, which radiated from the disk along the temporal vessel arcades and joined temporal to the macula. The optic disk, retinal vessels, periphery, and macula were normal in all patients. Visual function tests and fluorescein angiography indicated a segmental disease of the retinal pigment epithelium-photoreceptor complex.

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METASTATIC CHOROIDAL MELANOMA

DEVRON H. CHAR, M.D.
San Francisco, California

Because patients with metastatic choroidal melanomas usually survive less than one year after the diagnosis has been established, patients with pigmented choroidal lesions should be examined for metastatic disease before and after their initial ocular therapy.[1] Unfortunately, in patients with primary choroidal melanoma, it is unclear what constitues an adequate diagnostic examination for the detection of metastases.

Little data are available on the metastatic pattern of choroidal melanoma.[1,2] Whereas choroidal melanomas usually metastasize to the liver first, the incidence and the frequency of other metastatic occurrences is unclear. Some researchers report that as many as 98% of patients with metastatic choroidal melanomas have symptoms traceable to the liver or lungs.[3] We report herein the metastatic occurrences in choroidal melanoma patients examined betwen 1947 and 1977 at the University of California, San Francisco.

MATERIAL AND METHODS

We evaluated the medical records of all primary choroidal melanoma patients who had developed metastatic disease to ascertain the site of initial metastatic involvement, the sensitivity of the diagnostic assays used, and the interval between enucleation and the onset of metastatic disease, and between metastatic disease and death. The site of initial metastatic involvement was documented histologically. If a patient either had been treated elsewhere or had died at another institution, the physician responsible for his treatment was contacted, and whenever possible, the outside hospital record examined. Statistical analysis included the use of Student's t-test and chi-square tables.[4]

RESULTS

We studied 41 patients with a histologically verified diagnosis of metastatic choroidal melanoma. Twenty patients were women (mean age: 55 years old; range, 27 to 84 years old), and 21 patients were men (mean age, 54 years old; range, 26 to 74 years old). The interval between enucleation and onset of metastatic disease was 3.4 years in the men (range, two months to nine years) and 5.5 years in the women (range, 1 to 22 years). The difference was statistically significant ($P < .025$). The mean interval between the onset of metastatic disease and death was 1.3 years (range, one month to seven years).

Fifty-six percent of patients had either hepatic involvement (16) or the involvement of the liver and an additional organ system (seven) as a major primary manifestation of widespread disease (Table 1). The second most common manifestation of the disease that occurred in 36.5% (ten) of the patients involved subcutaneous tissue. Vertebral metastases occurred in three patients; other areas of initial metastatic disease were ovary, central nervous system, and pulmonary system.

Some diagnostic tests used in the examination of the patients appear in Table 2. In patients with metastases first noted in the liver, the majority had abnormal results with serum lactic dehydrogenase or alkaline phosphatase, or a positive liver-spleen scan. This group of patients gave

From the Ocular Oncology Unit, Department of Ophthalmology and the Francis I. Proctor Foundation, University of California, San Francisco. This study was supported in part by National Institutes of Health Grants EY02072, EY01759, and EY01441 and National Institutes of Health Research Career Development Award 1 K04 EY00117.

Reprint requests to Devron H. Char, M.D., S322, University of California Medical Center, San Francisco, CA 94143.

TABLE 1

INITIAL SITE OF METASTATIC DISEASE

Area of Involvement	No. of Patients
Liver involvement	16
Liver and skin involvement	2
Liver and pulmonary involvement	2
Liver and cental nervous system involvement	2
Liver and orbital involvement	1
Total number of patients with liver involvement as initial site of metastatic disease	23
Subcutaneous tissue involvement	10
Pulmonary involvement	2
Pulmonary and subcutaneous tissue involvement	1
Vertebral column involvement	3
Ovary involvement	1
Central nervous system involvement	1
Patients with extrahepatic involvement as initial site of metastatic disease	18

false-negative results with serum glutamic oxaloacetic transaminase or urinary melanogens at least 50% of the time. Metastatic involvement in most patients with extrahepatic disease was diagnosed initially by biopsy; however, in all cases of pulmonary disease, the chest X-ray suggested metastatic involvement.

DISCUSSION

Choroidal melanomas have a marked tendency to metastasize to the liver. In one series, at M.D. Anderson Hospital, 22 of 25 (88%) patients had hepatic involvement as the initial manifestation of metastatic disease[1]; in Denmark, approximately 61% of patients first went to their physicians with metastatic symptoms referrable to the liver.[2] In our study, 56% of patients had liver involvement as a first sign of widespread disease. The higher incidence of liver involvement observed at the M.D. Anderson Hospital probably is a result of the pattern of patient referral there. Physicians are more likely to refer patients with liver involvment to more

TABLE 2

RESULTS OF DIAGNOSTIC TEST*

Test	Liver	Extrahepatic
Alkaline phosphatase	13/15	1/8
Lactic dehydrogenase	6/7	2/5
Liver-spleen scan	7/9	0/4
Gastro-intestinal radiologic survey	2/5	1/7
Radiologic bone survey	1/5	2/7
Urinary melanogens	2/7	1/3
Bone marrow examination	0/3	1/4
Serum glutamic oxaloacetic transaminase	4/8	0/5
Brain scan	1/4	1/2
Routine chest roentgen	0/4	4/5

*Number of abnormal values/total number tested.

specialized institutions because the patients have a much poorer prognosis than those with metastases to other sites.[5]

Other common occurrences of metastatic disease include the development of subcutaneous nodules, bone pain (often with spinal cord compression), and pleural-pulmonary disease. In three of our patients, we noted central nervous system involvement (hemiparesis or papilledema) at initial diagnosis; however, two of the patients had concomitant hepatic metastases. Metastatic melanoma involving the nervous system often remains asymptomatic,[6] which was probably the case for two of three of our patients with central nervous system disease since they came to us with symptoms traceable to the liver. We observed one case with both orbital and liver metastases. Although orbital metastases are rare, both contralateral orbital involvement and contralateral metastases to the choroid have been known to occur.[7-9] Another unusual example of metastatic choroidal melanoma is involvement of the gastrointestinal tract either by obstruction or with bleeding.[6]

Patients with melanoma metastatic to the liver usually have increased serum alkaline phosphatase or serum lactic acid dehydrogenase. Unfortunately, many of our patients were examined before the routine use of the serum lactic acid dehydrogenase assay, which precluded determining the diagnostic accuracy of these tests. In a large series of patients with systemic metastatic melanoma, less than 2% with liver involvement had a normal serum lactic acid dehydrogenase, although in 46% of the patients, it was observed to be "falsely" increased by factors other than metastatic liver disease.[6] In that study, although lactic acid dehydrogenase yielded a higher incidence of false-positive results,[6] it proved more accurate than alkaline phosphatase in the detection of metastatic liver disease. N. Felberg (personal communication) has done preliminary work with another liver enzyme, gamma glutamyl transpeptidase, which may prove to be more accurate in diagnosing liver involvement than either the lactic acid dehydrogenase or alkaline phosphatase assay.

Because our patients developed metastatic disease between 1947 and 1977, many of them had confirmation of their diagnosis by biopsy without first having the currently available noninvasive diagnostic tests. In the present study, five of seven patients with liver involvement had positive liver-spleen scans. It is difficult to determine the relative sensitivity of liver-spleen scans as opposed to other diagnostic tests in the detection of metastatic disease. We observed two patients with confirmed metastatic liver lesions who had increased serum lactic acid dehydrogenase and normal scans. Previous work shows the incidence of false-negative scans in the detection of metastatic liver involvement to be between 20 and 80%.[10] This false-negative rate is probably due to the requirement that the metastatic tumor be at least 2 cm in size before it can be detected by either radioactive technetium or gallium scans.[10-12]

Two of seven patients with metastatic liver disease had positive urinary melanogens. Recent improvements in the methodology for the detection of melanin by-products in the urine suggest that the results of tests on urinary polyamines may correspond to the disease status in metastatic melanoma; however, a 20% false-negative rate occurs with these assays.[12,13]

To detect possible liver metastases in patients with choroidal melanoma, we routinely obtain a serum lactic acid dehydrogenase and serum alkaline phosphatase before ocular therapy, and every three months after the choroidal melanoma treatment at our ocular oncology unit.

If these test results are normal, we do no further liver function tests. However, if the blood tests are abnormal, a liver-spleen scan is performed; and, if the scan is equivocal, either an open biopsy or peritoneoscopy is performed.

All our patients undergo a complete physical examination because many of them first come to us with subcutaneous nodules as a manifestation of metastatic melanoma. Since all of our patients with pleural-pulmonary metastatic disease have shown changes on chest X-rays, we perform the test routinely on all patients. Although studies have described some patients with systemic malignant melanoma with metastatic lung lesions and negative plain films, we do not believe the incidence of this finding is sufficient to warrant the cost of obtaining routine chest tomography. Involvements of the central nervous or skeletal systems (especially the vertebral column) are less common manifestations of metastatic choroidal melanomas. We only obtain bone surveys, bone marrow examinations, or computed axial tomography on our patients when they have either bone pain or neurologic symptoms.

The usual interval between enucleation and the onset of metastatic disease is two to four years. We have observed the rare simultaneous occurrence of a primary melanoma of the choroid and metastatic lesions. Since the average life expectancy for patients with metastatic choroidal melanoma is about one year after the diagnosis of their disease, enucleation is probably inappropriate unless the eye is blind and painful. For this reason, as well as for the early detection and treatment of metastatic disease, we routinely perform the metastatic examination on all patients with choroidal melanomas before enucleation. Whereas most patients who develop metastatic disease had either mixed, necrotic, or epithelioid melanomas, 35% had primary spindle B tumors. Currently, I am working with immunologic tests to develop a better method of predicting which patients will develop metastatic disease.[14]

Summary

We studied the metastatic pattern of 41 patients initially referred with a primary choroidal melanoma who later developed widespread disease. In the order of frequency, the most common sites of metastatic involvement were the liver (56%), subcutaneous tissue (36.5%), and bone (7%). Whereas the median interval between enucleation and the onset of metastatic disease was approximately four years, in rare cases, metastases were diagnosed concurrently with a primary choroidal melanoma. Since patients with choroidal melanomas usually survive less than one year after the development of widespread disease, a metastatic examination should be done in all patients with pigmented choroidal tumors both before and after ocular therapy. From the data obtained in this and other studies on metastatic melanoma, a reasonable basic metastatic examination for choroidal melanoma patients should include a serum lactic dehydrogenase, a serum alkaline phosphatase, a routine chest X-ray, and a general physical examination.

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OPHTHALMIC MINIATURE

The name of Lady Hypatia Smythe-Browne (now Lady Hypatia Hagg) will never be forgotten in the East End, where she did such splendid social work. Her constant cry of "Save the Children!" referred to the cruel neglect of the children's eyesight involved in allowing them to play with crudely painted toys. She quoted unanswerable statistics to prove that children allowed to look at violet and vermilion often suffered from failing eyesight in their extreme old age. The devoted worker would tramp the streets untiringly, taking away the toys from all the poor children, who were often moved to tears by her kindness.

G. K. Chesterton, *Alarums and Discursions*
Methuen and Co., Ltd., 1910

CRYSTALLINE RETINOPATHY

W. SANDERSON GRIZZARD, M.D., AUGUST F. DEUTMAN, M.D., FRANS NIJHUIS, M.D., AND ALBERT AAN DE KERK

Nijmegen, The Netherlands

In 1937 Bietti[1] described three cases (two of which involved siblings) of a tapetoretinal degeneration characterized by (1) yellow glistening intraretinal crystals in the posterior pole, (2) tapetoretinal degeneration with sclerosis of the choroid, and (3) a crystalline dystrophy of the cornea. Further reports of this unusual dystrophy have been rare. However, in 1968 Bagolini and Ioli-Spada[2] reported six additional cases from Professor Bietti's eye clinic in Rome. All of these patients showed both corneal and ophthalmoscopic findings as previously described.

In 1977 François and DeLaey[3] reported two cases as Bietti's crystalline fundus dystrophy, but the patients failed to demonstrate the peripheral corneal changes that had been observed in the earlier cases.

Other researchers have also described patients with intraretinal crystals, choroidal atrophy, and pigment clumping in the periphery, but have not reported their cases as Bietti's crystalline fundus dystrophy (Table). We describe herein another patient with these characteristics in the fundus, but no corneal abnormalities.

SUBJECTS AND METHODS

The patient and her family underwent complete ophthalmologic examination including refraction, applanation tonometry, indirect ophthalmoscopy, biomicroscopic examination of the anterior segment, and contact lens examination of the posterior pole. Visual field examination was performed using the Goldmann perimeter. Color vision was tested with the AO-HRR pseudoisochromatic plates, a modified Farnsworth panel D-15, the 100-Hue test, and a Nagel II anomaloscope. The methods of electroretinography, electro-oculography, dark adaptation studies, and fluorescein angiography have been described in detail in previous reports.[4,5] Complete blood cell count, serum cholesterol, serum triglycerides, peripheral blood smear, and serum electrophoresis were done by routine laboratory methods. Serum and a 24-hour urine sample were analyzed for amino acids by using a Beckman/multichrome amino acid analyzer. Lipoprotein electrophoresis was performed by routine laboratory methods with a cellulose-acetate base.

CASE REPORT

A 34-year-old white woman came to the University Eye Clinic in Nijmegen complaining of slowly diminishing visual acuity. She had not experienced night blindness or photophobia. She had no history of kidney disease or other serious illnesses. The patient was one of six children of a consanguineous marriage (Fig. 1). The family history was noncontributory for eye disease.

Her visual acuity was 6/9 (20/30) in both eyes. The cornea was normal, as was the intraocular pressure. The vitreous was clear. Although there were no peripheral stromal crystals, ophthalmoscopic examination revealed in the posterior pole, confined to the major temporal vascular arcades, numerous glistening crystals one-half to one-third the size of a vessel at the disk. There was marked loss of pigment epithelium and choriocapillaris and pigment clumping in the fovea. Peripheral retricular pigmentation resembled senile reticular pigment degeneration,[6] although it did not invade the retina along the veins as in retinitis pigmentosa. The crystals appeared in the inner and middle retinal layers. The pigment epithelium and choroid were preserved in the fovea. The disk appeared normal in color and size, and the retinal vessels were not attenuated (Figs. 2 and 3).

Electrophysiologic testing showed a normal electroretinogram with normal cone and rod function as measured by dark adaptation, flicker, and red and

From The Institute of Ophthalmology, University of Nijmegen, Nijmegen, The Netherlands.

Reprint requests to August F. Deutman, M.D., the Institute of Ophthalmology, University of Nijmegen, Philips van Leydenlaan 15, Nijmegen, The Netherlands.

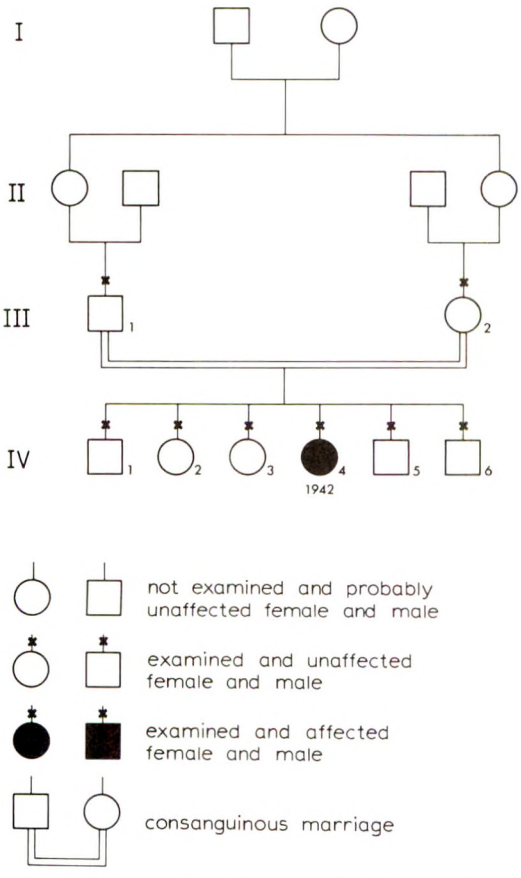


Fig. 1 (Grizzard and associates). Pedigree of consanguinity of the parents of the proband with crystalline dystrophy. Autosomal recessive inheritance is probable.

blue stimuli. The electro-oculogram was flat with no rise during light adaptation. The color vision studies showed a mild red-green defect with the AO-HRR plates, the panel D-15, and the 100-Hue test. The Nagel II anomaloscope showed decreased red sensitivity. The visual fields revealed bilateral annular scotomas. Dark adaptation studies showed a slightly delayed rod adaptation of 0.5 log units. Fluorescein angiography demonstrated partial loss of the choriocapillaris and pigment epithelium. The crystals neither accumulated nor transmitted fluorescein. There were prominent areas of circular, well defined choriocapillaris atrophy and larger areas of pigment epithelial loss (Figs. 4 and 5).

On examination, the siblings and parents were found to be normal. The parents underwent electro-oculography. The father had a slightly reduced light to dark ratio in both eyes (R.E.: 1.50; L.E.: 1.78): the mother had decreased light rise in the left eye only (R.E.: 1.96; L.E.: 1.68). (Normal ratio is 1.85.)

The hematocrit was 44%. No acanthocytosis was seen. Amino acid analysis of urine and serum was normal. Serum cholesterol was 6.09 mM/l (normal, 4.7 to 7.5). Serum triglycerides were 1.04 mM/l (normal, 0.8 to 2.0). Lipoprotein electrophoresis in the patient showed a slightly increased alpha fraction, normal pre-beta fraction, and a slightly reduced beta fraction, whereas it was normal in both parents.

Discussion

In the cases of ophthalmoscopically visible crystals in the retina, described by Bietti[1] and Bagolini and Ioli-Spada,[2] the fundus showed a "crystalline and glittering" retinopathy with bone corpuscle pigmentation in the periphery and ap-

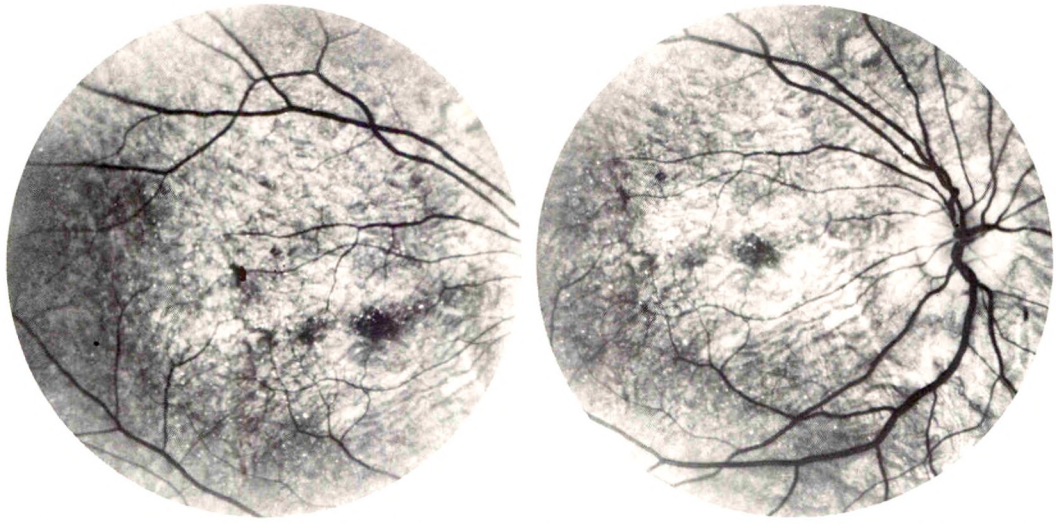


Fig. 2 (Grizzard and associates). Left, Right posterior pole with many white crystals localized in the inner and middle retinal layers. Disk and vessels are normal. Right, There is also atrophy of the retinal pigment epithelium and choriocapillaris.

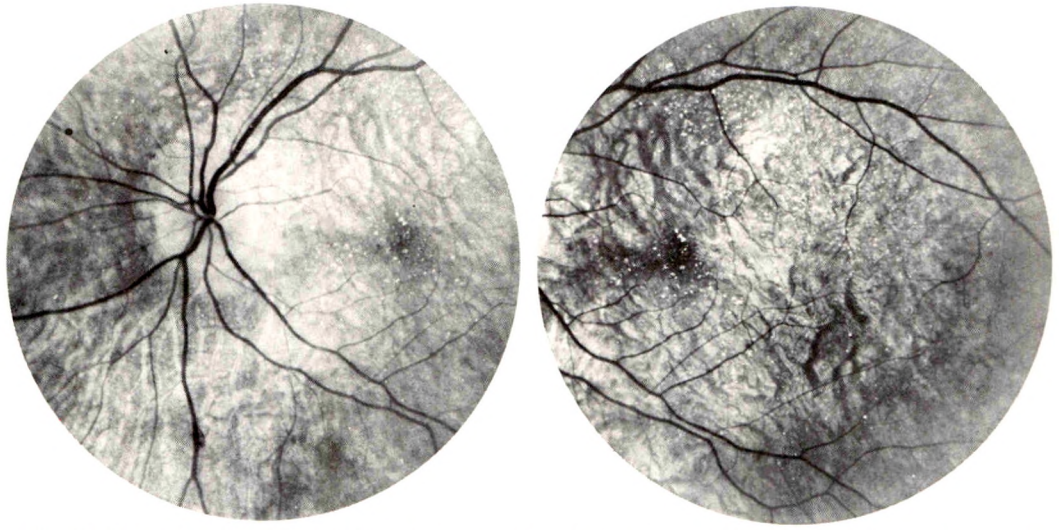


Fig. 3 (Grizzard and associates). Left, Left posterior pole with essentially the same abnormalities as the right posterior pole (right).

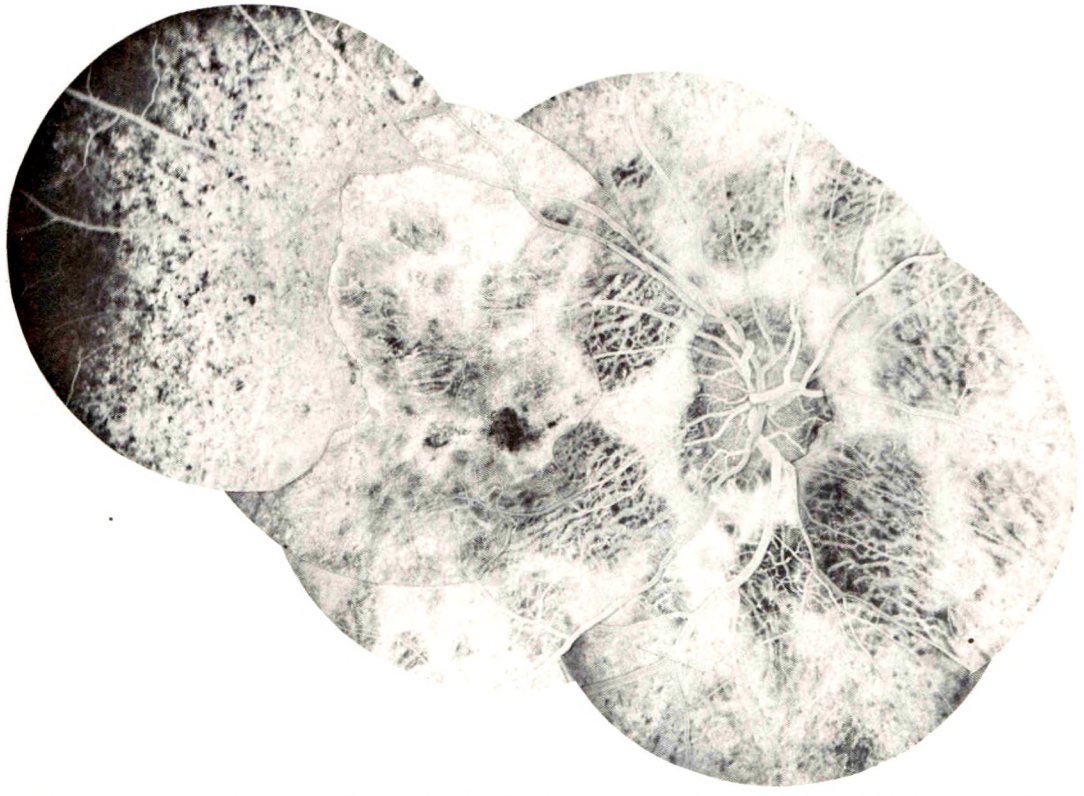


Fig. 4 (Grizzard and associates). Composite study of fluorescein angiograms of the right fundus. The fovea is still relatively intact. Around the disk there are many circular areas of choriocapillaris and retinal pigment epithelial atrophy. In the midperiphery there is a mottled pattern of hyperfluorescence, but the far retinal periphery is normal.

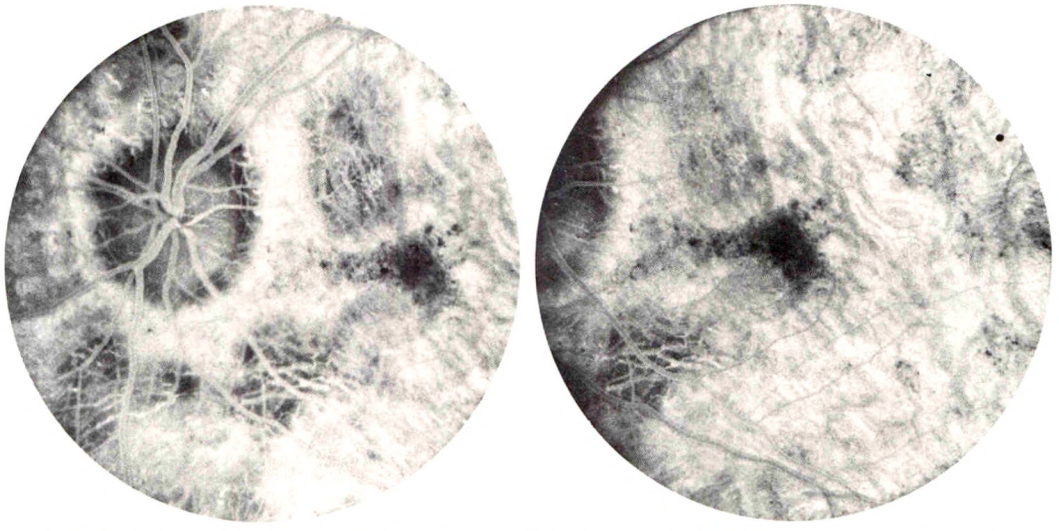


Fig. 5 (Grizzard and associates). Left, Fluorescein angiogram in a later stage of the left eye showing essentially the same abnormalities as the right eye (right). The crystals do not accumulate fluorescein.

peared brownish. All patients had a peculiar peripheral crystalline corneal dystrophy. The visual acuity in the previously mentioned nine cases varied from 6/6 (20/20) to 6/300 (1/50). Six of nine patients complained of night blindness. The electroretinograms were unrecordable or electronegative (a-wave greater than b-wave) in all patients except for one who had a normal response when initially examined at 28 years of age. The composition of the crystals was not determined, and no systemic metabolic disturbances were found. Two patients, however, had slightly increased esterfied cholesterol levels.

In 1970 Craandijk and Houtsmuller[7] reported a case of hypo-beta-lipoproteinemia in a 45-year-old woman who had a fundus picture similar to that of our case. The patient complained of loss of vision in one eye and night blindness. The visual acuity was not reported, but the fundus had a central retinal dystrophy with a shiny, silvery central retina. The posterior pole was covered with shiny yellow crystals. The fundus pictures and fluorescein angiograms demonstrated changes similar to those in our patient. The electroretinogram showed normal photopic responses and scotopic responses within the lower limits of normal. The electro-oculogram was reported as "probably normal."

In 1977 Noble, Carr, and Siegel[8] reported a case of a "peripapillary choroidal dystrophy" almost identical to our case and that reported by Craandijk and Houtsmuller.[8] The patient's fundus showed multiple areas of pigmentary loss and choriocapillaris atrophy and striking posterior pole crystals in the retina. The electroretinogram and electro-oculogram were normal and the vision was good. The peripheral dark adaptation was normal.

In 1977, François and DeLaey[3] reported two cases of Bietti's crystalline fundus dystrophy (Biettische kristalline Fundus-dystrophie). One patient had consanguineous parents, and both patients had a crystalline retinal dystrophy with atrophy of the choriocapillaris and pigment epithelium. The vision in one eye of one

patient was greatly reduced because of macular degeneration, but that patient's other eye had a visual acuity of 6/7.5 (20/25). The other patient's visual acuity was R.E.: 6/15 (20/50); L.E.: 6/30 (20/100). Neither patient complained of night blindness. The electroretinogram was subnormal in one patient and electronegative in the second patient. One electro-oculogram was flat and the other subnormal. Neither patient had corneal crystals. Other reports on this condition were presented by Gass[9] and Welch.[10]

Ophthalmoscopically visible crystals in the posterior pole have also been reported in oxalosis (for which the genes are recessive), and these crystals are more likely to occur in primary oxalosis than in the secondary forms caused by kidney failure, toxins such as ethylene glycol, thiamine deficiency, and spinach or rhubarb gluttony.[11] To our knowledge, electrophysiologic studies have not been performed for this condition.

Oxalate crystals have also been reported in the retina of eyes with long-standing detachments.[12,13] Garner[12] has speculated that local disturbances of metabolism caused by retinal detachment could lead to the deposition of such crystals. If this is true, a pigment epithelial or choroidal dystrophy might also cause the formation of such crystals in the retina.

Takki[14] noted numerous glistening crystals scattered throughout the equator in the most advanced stage of gyrate atrophy of the choroid, which is associated with hyperornithinemia[14,15] and is inherited recessively. Kurstjens[16] found varying subnormal or extinguished electroretinograms and usually severely affected electro-oculograms in this disease.

Serum and urine ornithine levels in our patient were normal. We considered that our patient might be a severely affected carrier of choroideremia. Clinical manifestations of the carrier state vary from a severely affected fundus, as in the affected male, to a normal appearing eye. In view of the noncontributory history for the disease in this large family, the normal results of the examination of the mother and the other siblings, and the definite consanguinity of the parents, our hypothesis seems unlikely.

In cystinosis, a recessively inherited metabolic disorder, corneal crystals and a pigmented dystrophy of the fundus also occur.[17] The corneal crystals, however, involve the entire cornea, and the ophthalmoscopically visible crystals reported by Donaldson[18] were located in the choroid only. Histopathologic studies in cystinosis showed crystals in the choroid and pigment epithelium, but none in the retina.[19]

The ophthalmoscopically striking crystals that are evident in several diversified disorders probably occur secondarily to a metabolic disturbance in the pigment epithelium-photoreceptor complex. The exact composition of the crystals remains unknown, but we must consider the possibility that their development is related to the crystals seen in longstanding retinal detachment or to a disorder of lipid metabolism. Lipid abnormalities were noted in several patients, but present techniques have not revealed any common abnormality of the lipoproteins.

Because the metabolic defect that causes crystalline retinopathy is not well defined, it is unclear whether all crystalline dystrophies have a common etiology or only a clinical similarity. Until the underlying metabolic defect is identified, we must bear in mind that crystalline retinal dystrophy has been reported both with and without corneal crystals, and with varying clinical and electrophysiologic findings (Table).

SUMMARY

A 34-year-old woman had crystalline dystrophy of the retina associated with atrophy of the choriocapillaris and pig-

TABLE

SUMMARY OF CLINICAL AND ELECTROPHYSIOLOGIC FINDINGS IN CRYSTALLINE RETINOPATHY

Author	Case No.	Age (yrs)	Sex	Visual Acuity	Visual Fields	Corneal Crystals	Additional Fundus Findings*	Electro-retinogram	Electro-oculogram	Remarks
Bietti[1]										
	1	31	M	6/15 (20/50) 6/9 (20/30)	Constricted	Yes	Disks and vessels normal	Electro-negative	NA	Case Nos. 1 and 2 are brothers
	2	26	M	6/30 (20/100) 6/9 (20/30)	Constricted	Yes	Disks and vessels normal	Absent	NA	
	3	30	M	6/300 (1/50) 6/300 (1/50)	Ring scotoma	Yes	Slightly pale disks, vessels normal	NA	NA	Increased serum cholesterol
Bagolini and Ioli-Spada[2]										
	4	36	M	6/150 (2/50) 6/75 (4/50)	R.E.: central scotoma; L.E.: constricted	Yes	Disks and vessels normal	Absent	NA	Increased serum cholesterol; case Nos. 4 and 5 are brothers
	5	44	M	6/15 (20/50) 6/9 (20/30)	Constricted	Yes	Disks and vessels normal	Absent	NA	Increased serum cholesterol
	6	31	F	No light perception Light perception	NA†	Yes	Retinal detachment	Absent	NA	Crystals may be secondary to retinal detachment
	7	37	M	6/60 (20/200) 6/60 (20/200)	NA	Yes	Disks pale, vessels normal	Absent	NA	
	8	28	F	6/6 (20/20) 6/6 (20/20)	Normal	Yes	NA	Normal	NA	Consanguineous parents

Craandijk and Houtsmuller[7]	9	41	M	6/300 (1/50) 6/150 (2/50)	Constricted	Yes	Normal disks and vessels	Absent	NA	
	10	45	F	NA	Minor loss of central field	No		Normal	Normal	Consanguineous parents; hypobetalipoproteinemia
Noble, Carr, and Siegel[8]	11	54	M	6/9 (20/30) 6/6 (20/20)	NA	NA		Slightly subnormal	Normal	Consanguineous parents
François and DeLaey[3]	12	19	M	6/15 (20/50)	Central scotoma	No	Disks and vessels normal	Subnormal	Flat	Consanguineous parents; increased serum triglycerides, pre-beta lipoproteins, and chylomicrons
	13	35	F	6/300 (1/50) 6/7.5 (20/25)	Cecocentral scotoma, R.E.	No	Disks and vessels normal	Electronegative	Subnormal	
Present study	14	34	F	6/9 (20/30) 6/9 (20/30)	Ring scotoma	No	Disks and vessels normal	Normal	Flat	Consanguineous parents; abnormal serum protein electrophoresis

*Retinal crystals, choroidal atrophy, and pigment clumping in the periphery occurred in all cases.

†Information not available in report.

ment epithelium, and pigment clumping in the fundus periphery. Consanguinity of her parents suggested an autosomal recessive inheritance pattern for this type of crystalline retinal dystrophy. The patient did not have corneal crystals. Her electroretinogram was normal, although her electro-oculogram was abnormal.

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A SIMPLE TECHNIQUE FOR REMOVAL OF RECURRING GRANULAR DYSTROPHY IN CORNEAL GRAFTS

STEVEN L. LEMPERT, M.D., MARK S. JENKINS, M.D., BRUCE L. JOHNSON, M.D., AND STUART I. BROWN, M.D.

Pittsburgh, Pennsylvania

Three studies describing the light and electron microscopic appearance of seven regraft specimens have focused on recurrences of granular corneal dystrophy in grafted corneas.[1,2,3] In one of the specimens, the recurrence appeared throughout the stroma. The recurrence of the dystrophy in the other six specimens was localized in an avascular fibrous tissue between the epithelium and Bowman's layer. We describe herein a quick, simple technique for the excision of the anterior opaque layer of tissue recurring in granular dystrophy in otherwise transparent corneal transplants.

SUBJECTS AND METHODS

In 1968, a 54-year-old man and his 15-year-old son each related a similar history of a slowly progressing decrease in visual acuity beginning at approximately 3 years of age. The left eye of the father had been destroyed in a concentration camp during World War II. The father's right eye had a visual acuity of finger counting at one foot, whereas the son had 6/30 (20/100) in each eye. The corneas of both patients had diffuse anterior stromal opacifications that did not involve the periphery and were characteristic of granular dystrophy. During that year, 7.5-mm partial-penetrating corneal transplants were performed on the right eye of the father and both eyes of the son. The grafts remained transparent, and the corrected visual acuities were 6/18 (20/60) in the father's eye and 6/12 (20/40) in each of the son's eyes. Light and electron microscopic examination of the corneas excised at surgery corroborated the clinical diagnosis.[4]

When the patients were examined again in 1971, they had recurrences of the granular dystrophy in the most superficial portion of the three grafted corneas. The visual acuity at that time was 6/60 (20/200) in the father's right eye and 6/24 (20/80) in each of the son's eyes. In July 1977 the visual acuity was finger counting at four feet in the father's right eye and 6/240 (10/400) in each of the son's eyes. The opacifications had remained superficial and were more opaque than at the previous examination (Fig. 1). A repeat 7.5-mm partial-penetrating corneal transplant was performed on the son's right eye on July 7, 1977. The postoperative course was uneventful, and the graft remained transparent. Histologic examination of the cornea removed at the repeat transplantation showed numerous sharply delineated hyaline deposits within an

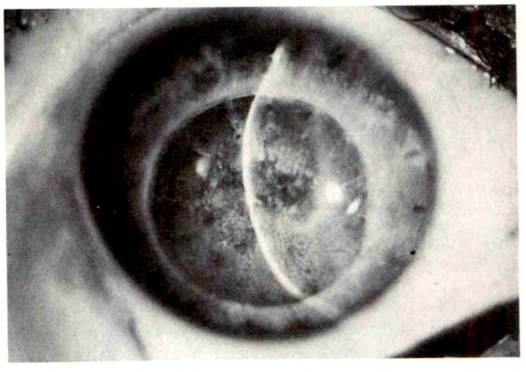


Fig. 1 (Lempert and associates). Recurrence of granular dystrophy in the corneal graft of the son's left eye.

From the Department of Ophthalmology, University of Pittsburgh School of Medicine, and Eye and Ear Hospital, Pittsburgh, Pennsylvania.

Reprint requests to Stuart I. Brown, M.D., Department of Ophthalmology, Eye and Ear Hospital, 230 Lothrop Street, Pittsburgh, PA 15213.

avascular connective tissue band interposed between the corneal epithelium and Bowman's layer (Fig. 2). The affected areas stained a brilliant red with the Masson trichrome stain and were less PAS-positive and less birefringent than the uninvolved connective tissue.

Because the recurrence of granular dystrophy did not involve the corneal stroma, the patients were advised about the possibility of removal of the opacified anterior layer only rather than a penetrating or lamellar corneal transplant. The procedure was performed first on the son's left eye by means of topical anesthesia. Corneal forceps were used to fix the globe and the opaque layer was incised by scraping with the back of a razor blade until a smooth, glass-like surface, presumably Bowman's layer, was exposed. The opaque layer was initially scraped free of the smooth surface until we realized that it could be lifted from the cornea, which created a small pocket that allowed the entrance of the tip of a cyclodialysis spatula. The spatula was rotated to bluntly dissect the opaque layer to the graft-host interface where it was excised. A faint opacification remained where the cornea was initially scraped. The epithelium healed over the graft in five days, and, in spite of the mentioned opacification, the corrected visual acuity was 6/12 (20/40), which was equal to the best visual acuity after the first corneal graft. The experience with removal of the opaque dystrophic layer from the son's eye facilitated the operation in the father's eye. After topical anesthesia was applied to the father's eye, the back of a razor knife was used to scrape through the tough opaque layer, exposing the glassy-smooth Bowman's layer near the host-graft interface. The opaque layer was lifted with forceps, creating a pocket into which a cyclodialysis spatula was passed. The membrane was bluntly dissected from the graft and excised. The procedure took less than two minutes. No opacification remained. The corneal epithelium healed in five days and the visual acuity was 6/15 (20/50). There has been no obvious invasion of dystrophic tissue onto the grafts in the two eyes during a four-month follow-up period (Fig. 3). The histopathologic appearances of the excised layers did not contain Bowman's layer (Fig. 4) and were similar to those seen in front of Bowman's layer on the corneal button removed during the son's corneal transplant.

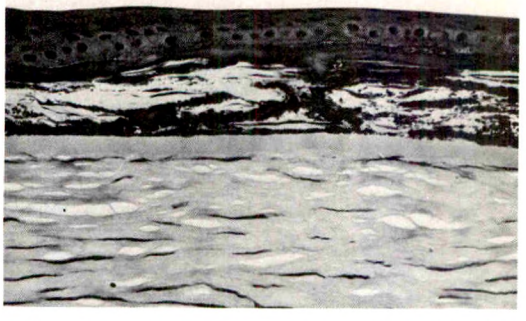


Fig. 2 (Lempert and associates). Extensive discrete dark staining (red) granular deposits are present within an avascular connective tissue membrane anterior to an intact Bowman's layer. The stroma is free of deposits (Masson trichrome, × 120).

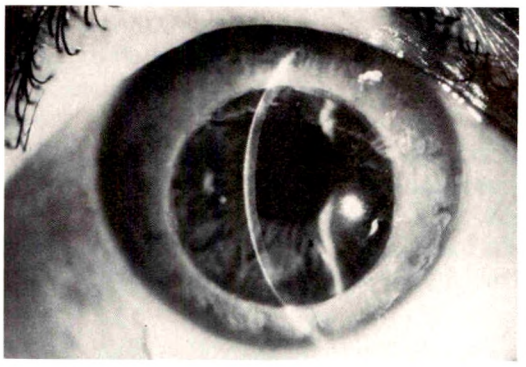


Fig. 3 (Lempert and associates). Appearance of the son's left cornea three weeks after removal of the anterior membrane.



Fig. 4 (Lempert and associates). Numerous aggregates of finely granular deposits are present throughout the subepithelial connective tissue band. These extend to the deep border of the specimen and no Bowman's layer is included (2-μ section, toluidine-blue, × 300).

Discussion

The results of this study reinforce earlier findings that recurrences of granular dystrophy in grafted corneas usually take the form of an avascular connective tissue layer in front of Bowman's layer of the graft. The connective tissue layer containing deposits that had the histochemical staining pattern of granular dystrophy was easily separated from the underlying glassy-appearing Bowman's layer and excised. Although it is certainly possible that the dystrophy could recur again, it is also likely that the opaque layer of tissue could be easily removed with the technique we described.

The dystrophic material probably cannot penetrate Bowman's layer since it remained in front of it for years. The keratocytes, rather than the epithelium, probably are the cells responsible for the deposits since they are characteristically found in the stroma of the unoperated cornea.

Summary

A 63-year-old man and his 24-year-old son developed recurrences of granular dystrophy in their three corneal grafts within three years after surgery. We regrafted one of the son's corneas. Histologic examination of the corneal button removed during surgery showed an avascular connective tissue layer with the histochemical characteristics of granular dystrophy interposed between the epithelium and Bowman's layer. In the remaining two corneal grafts, we fixed the globe with corneal forceps and removed the opaque dystrophic layer by separating it it from the cornea with a spatula. Postoperatively, all three corneal grafts were once more transparent.

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A LIGHT MICROSCOPIC STUDY OF GROUND SUBSTANCE CHANGES IN ALKALI-BURNED CORNEAS

CECIL V. CRABB, M.D.
Winston-Salem, North Carolina

Retrocorneal fibrous membranes have been observed after penetrating keratoplasty and various forms of trauma, including chemical burns and thermal injury. We present herein light microscopic data that revealed changes in the acid mucopolysaccharide ground substance of retrocorneal membranes secondary to alkali burns as compared to the evolution of acid mucopolysaccharide staining characteristics noted at the primary burn site.

MATERIAL AND METHODS

Using a filter paper disk saturated with 4N sodium hydroxide as detailed in a previous study,[1] we gave 33 New Zealand white albino rabbits 7-mm central corneal burns. Eyes were enucleated and corneas embedded in paraffin at 0.5, one, 1.5, six, eight, and nine weeks post burn. Three ground substance stains were used. The PAS reagent relies on oxidation of hydroxyl groups in sugars and subsequent bonding of the resulting adjacent aldehydes with a red dye molecule to demonstrate the presence of neutral mucopolysaccharides and nonsulfated acid mucopolysaccharides. In the Alcian blue staining method, a copper phthalocyanin dye complex is used to specifically bind acid mucopolysaccharides. A more intense blue staining of substituted acid mucopolysaccharide is produced with colloidal iron reagent that specifically attaches ferric iron to phosphate and sulfate groups of acid mucopolysaccharides. This ferric iron is then exposed for light microscopy with potassium ferrocyanide in the classical prussian blue reaction. Hematoxylin and eosin, alkaline congo red, Masson's trichrome, Verhoff-Van Gieson, and silver methenamine stained sections were also obtained. Histochemical changes observed with these agents were compared to reactions obtained from three uninjured rabbit eyes.

RESULTS

All corneas in this series displayed extensive edema that gradually, but incompletely resolved during the course of the nine-week study.

One week post burn, a retrocorneal membrane was easily identifiable in all 29 alkali-burned corneas. One hundred percent of these lesions displayed markedly positive colloidal iron and Alcian blue staining. The PAS reactivity of all retrocorneal fibrous membranes examined before six weeks post burn, however, was less than that of a normal cornea.

Sections obtained at six weeks post burn exhibited further enlargement of the retrocorneal membranes and markedly positive colloidal iron (Fig. 1) and Alcian blue reactions relative to those of an unburned cornea. Two thirds of the six-week specimens continued to show decreased PAS reactivity in the retrocorneal fibrous membrane, whereas one third revealed increased PAS staining relative to the surrounding unburned cornea. Eight- and nine-week sections disclosed continued membrane expansion and colloidal iron/Alcian blue positivity. Seventy-five percent of eight-week retrocorneal fibrous membranes, and 85% of nine-week specimens displayed increased PAS reac-

From the Department of Ophthalmology, University of North Carolina School of Medicine, Chapel Hill, North Carolina, and McPherson Hospital, Durham, North Carolina.

Reprint requests to Cecil V. Crabb, M.D., Department of Ophthalmology, University of North Carolina School of Medicine, 617 Clinical Sciences Building, Chapel Hill, NC 27514.

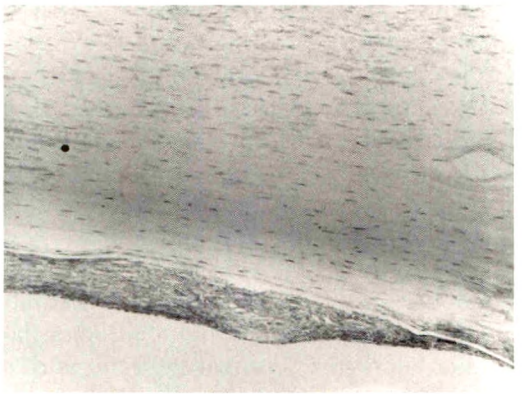


Fig. 1 (Crabb). Retrocorneal fibrous membrane at six weeks post burn. Note prominent increase in colloidal iron staining relative to adjacent unburned cornea (colloidal iron-nuclear fast red, × 120).



Fig. 3 (Crabb). Cornea at four days post burn. Colloidal iron staining reveals diffuse reaction in burned zone. Arrows denote margin of staining (colloidal iron-nuclear fast red, × 25).

tions (Fig. 2) relative to the adjacent unburned cornea. Retrocorneal membranes expanded progressively during the nine-week study, and all retrocorneal fibrous membranes contained a ground substance that reacted strongly with colloidal iron and Alcian blue stains relative to unburned corneal regions and to unburned controls. The PAS staining of the ground substance within these retrocorneal fibrous membranes gradually increased as the lesions evolved and exceeded the PAS reactivity of the surrounding unburned cornea in a majority of eyes during the eighth to ninth weeks post burn.

During the initial two weeks after injury, colloidal iron staining revealed diffuse positivity of the burned zone (Fig. 3). By six weeks, however, several changes were apparent in the configurations of colloidal iron reactions. Intense colloidal iron positivity appeared in the outer third of the burned stroma (Fig. 4). Mild colloidal

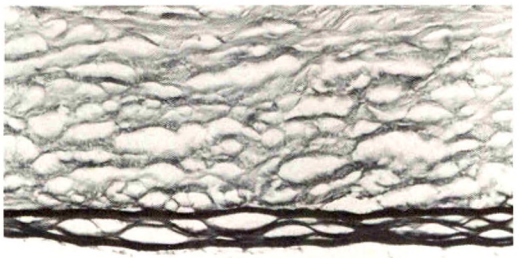


Fig. 2 (Crabb). Retrocorneal fibrous membrane at eight weeks post burn. PAS positivity relative to adjacent unburned cornea is apparent (PAS, × 400).

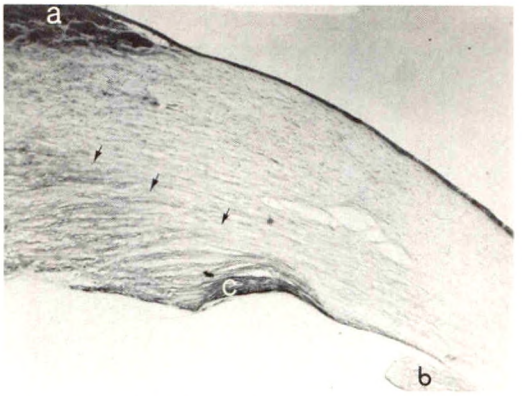


Fig. 4 (Crabb). Six-week specimen demonstrates intense acid mucopolysaccharide reaction in stromal scar (a), spread of acid mucopolysaccharide staining (arrows) in a triangular configuration away from the scar, and colloidal iron positive retrocorneal fibrous membrane at margin of the triangular stain (b). Compression artifact is noted (c) (colloidal iron-nuclear fast red, × 25).

iron reaction spread from that zone of extreme positivity in a pattern resembling a triangle, the base of which was formed by Descemet's membrane (Figs. 4 and 5). Of the nine retrocorneal fibrous membranes detected during that stage, seven were located at the margins of this colloidal iron-positive triangle. By eight to nine weeks post burn, this cone-shaped extension of colloidal iron positivity disappeared, and strong acid mucopolysaccharide staining was now confined to the outer one third of the originally burned stroma.

The PAS staining in the zone of the original burn also underwent temporal changes. Specimens obtained during the initial six weeks following injury yielded PAS reactions that were similar to those of the surrounding unburned cornea. Six weeks post burn, however, 75% of alkali-induced scars were less PAS-reactive than the surrounding unburned cornea.

Masson trichrome and silver methenamine stains were markedly positive for new collagen fibers both within corneal scars and retrocorneal fibrous membranes. Alkaline congo red and Verhoff-Van Gieson stains were negative for amyloid and elastin, respectively, in all tissues examined.

One PAS section (Fig. 6) was particularly interesting because it revealed a small break in Descemet's membrane within the alkali-burned zone. Regularly arranged stroma observed anterior to this defect bridged the gap and spread over the posterior surface of Descemet's membrane. Parallel arrangement of the retrocorneal fibrous membrane collagen lamellae and the corneal stroma and a smooth transition across the Descemet's break suggest that this particular retrocorneal fibrous membrane was of stromal origin. Because light microscopy revealed fraying and irregularity of Descemet's membrane in this section and electron microscopic study of cell fine structure in these lesions has already been reported,[2] electron microscopy of this region was not performed.

Discussion

The temporal sequence of retrocorneal fibrous membrane development as observed in our series agrees with previous reports[2] noting onset of retrocorneal fibrous membrane development at three to

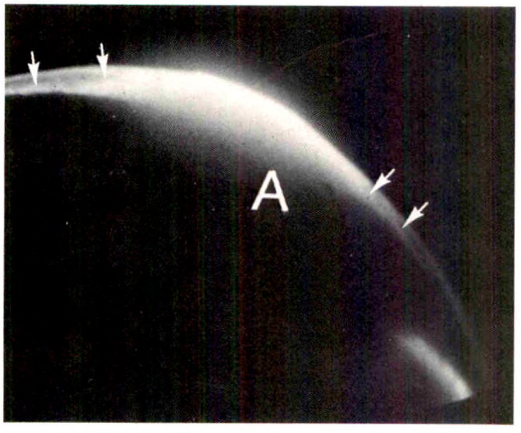


Fig. 5 (Crabb). Slit-lamp photograph at six weeks. Note edema, neovascularization (A), and spread of opacification (arrows) in pattern corresponding to the triangular configuration of acid mucopolysaccharide staining seen in Figure 4 (× 25).

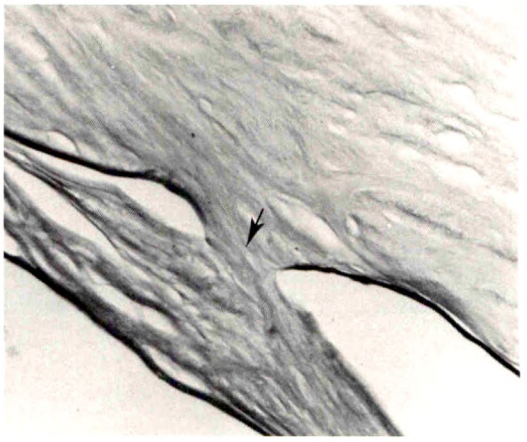


Fig. 6 (Crabb). Note break in Descemet's membrane (arrow), with stromal tissue penetrating the defect and merging with a retrocorneal fibrous membrane (PAS, × 400).

four days post burn with progressive enlargement thereafter. We observed that 100% of 33 retrocorneal membranes secondary to alkali burns exhibited prominent, early, and sustained colloidal iron/Alcian blue positivity, and that a majority of retrocorneal fibrous membranes gradually acquired enhanced PAS reactivity relative to unburned sections of the same corneas and to unburned controls. These findings conflict with an earlier study[3] that stated retrocorneal fibrous membranes stain identically to normal corneal stroma. This discrepancy could be explained by these authors' failure to use colloidal iron or Alcian blue stains in their evaluation.

We believe that the histochemical changes seen in our retrocorneal fibrous membranes represent alterations of the corneal ground substance rather than artifactual degeneration secondary to alkali exposure. Electron microscopic evidence[2] of new collagen and basement membrane material synthesis by "fibroblast-like" cells within these lesions corroborates our viewpoint. As each membrane enlarges, colloidal iron/Alcian blue staining expands uniformly and simultaneously. This observation suggests that the altered acid mucopolysaccharide reactivity constitutes an intrinsic component of newly synthesized tissue. Anseth[5,6] has demonstrated synthesis of dermatan sulfate, a mucopolysaccharide foreign to the normal cornea, during the evolution of corneal scars. Colloidal iron/Alcian positivity of the retrocorneal membranes in our series may reflect accumulation of the same material.

In contrast to the uninterrupted expansion of the retrocorneal fibrous membrane and its uniform colloidal iron/Alcian blue reactivity mentioned previously, the corneal scar exhibits distinct phases of ground substance staining. Early diffuse staining within corneal burns probably represents artifactual (alkali-induced) degradation of ground substance because it is difficult to imagine how a stroma that is hypocellular in the immediate post burn period could produce increased amounts of acid mucopolysaccharide. Subsequent triangular spread of acid mucopolysaccharide reactivity from a strongly staining corneal scar could reflect a combination of prior degenerative changes and superimposed synthesis and rearrangement of ground substance by infiltrating fibroblasts. The final phase, in which colloidal iron/Alcian blue staining is confined to the outer one third of the burned stroma, illustrates continued reorganization of acid mucopolysaccharide matrix material. The histochemical appearance of corneal scars post alkali burn, therefore, represents a mixture of probable early degenerative changes followed by syntheses and rearrangement of acid mucopolysaccharide ground substance.

The pathogenesis of retrocorneal fibrous membranes is debatable. Infiltrating fibrogenic cells of host origin[6] have been identified as principal contributors to the lesion following keratoplasty. Reports that retrocorneal fibrous membranes could arise behind an apparently intact Descemet's membrane[7] and studies[2,8] producing "fibroblast-like" cells cast considerable doubt on an earlier proposal[3,9] that stated stromal fibroblasts penetrated breaks in Descemet's to initiate retrocorneal membranogenesis. The possibility exists, however, that small defects in Descemet's membrane and a resulting infiltration of stromal tissue may have been missed in the studies that advocate an exclusively endothelial origin for retrocorneal fibrous membranes. We present evidence (Fig. 6) of such a break in Descemet's membrane, with stromal invasion through the defect, in an eye that received only noninvasive chemical trauma. This histologic section suggests that endothelial and stromal mechanisms of retrocorneal membranogenesis

may both be operative, either alone or in combination.

The significance of these results is at least twofold. First, there is a correlation between biochemical data on altered acid mucopolysaccharide in corneal wounds[4,5,10] and histopathologic observations. Second, factors that favor production of the abnormal ground substance reactivity detected histologically in this study and biochemically in others[4,5] may be identified. Corneas in our series displayed a pathologic tetrad of edema, at least one incidence of nonpenetrating rupture of Descemet's membrane, changes in acid mucopolysaccharide content (of both scars and retrocorneal fibrous membranes), and opacification. Research on fetal corneas[11,12] demonstrates marked changes in acid mucopolysaccharide composition and degree of sulfation associated with a sudden decrease in stromal water content and increased transparency around the time (day 14) at which Descemet's membrane is completed. Dedifferentiation of endothelium and keratocytes following corneal injury may place them in a state of morphological and functional identity with their embryonic precursors. If that were the case, these primitive cells could secrete a ground substance similar to that which characterizes the early overhydrated, opaque phase of corneal development. Knowledge of these interactions and how to manipulate them might improve our ability to preserve keratic transparency compromised by trauma, disease, or surgery or all three.

Summary

Retrocorneal fibrous membranes occurred in 100% of 33 rabbit eyes burned with 4N sodium hydroxide. All membranes exhibited markedly positive colloidal iron/Alcian blue ground substance staining relative to unburned sections of the same corneas and to normal controls. Retrocorneal fibrous membranes also gradually acquired PAS reactivity greater than either unburned sections of the same corneas or uninjured eyes. Colloidal iron/Alcian blue reactivity of retrocorneal fibrous membranes was similar to that which developed in the alkali-induced stromal scars. One histologic section revealed retrocorneal membranogenesis by stromal components that had penetrated a small alkali-induced break in Descemet's membrane.

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INTRAOCULAR PRESSURE AND CORNEAL THICKNESS AFTER PENETRATING KERATOPLASTY

RANDALL J. OLSON, M.D., AND HERBERT E. KAUFMAN, M.D.
New Orleans, Louisiana

Increased intraocular pressure (IOP) is commonly thought to lead to corneal swelling. Harris, Gehrsitz, and Gruber[1] reported corneal swelling as a common occurrence in the normal eye, and Lowe[2] cited it as an aggravating factor in acute glaucoma. Experimental work, however, by Ytteborg and Dohlman[3,4] failed to show much, if any, change in stromal thickness with increased pressure. Ehlers,[5–7] and Ehlers and Riise[8] observed a stromal thinning with increased pressure.

We observed corneal thickness at many pressure levels after aphakic keratoplasty and keratoplasty combined with cataract extraction,[9] and discovered that pressures above 60 mm Hg are typically associated with a thin, crystal-clear cornea. Furthermore, we believe that increased IOP may lead to stromal thinning, at least during the first week after keratoplasty.

SUBJECTS AND METHODS

All patients who underwent penetrating keratoplasty at the University of Florida from May 10, 1977, to Aug. 25, 1977, were included in our test. During each day of the postoperative week, stromal thickness was measured by Haag-Streit pachometry, and IOP was measured by Mackay-Marg applanation tonometry. From our findings, we divided the patients into two groups. Group 1 was composed of patients who had an IOP range during the first postoperative week of at least 20 mm Hg (Table 1). Group 1 was further subdivided into high range and low range: the high range represented corneal thicknesses recorded when the IOPs were highest, and the low range represented corneal thicknesses of the same patients when their IOPs were at least 20 mm Hg lower. We entered the same number of high and low pressure range measurements for each patient so that the two subgroups of high range and low range were carefully matched. Patients in Group 2 had a pressure range of 10 to 19 mm Hg, and the group was further subdivided by high range and low range findings. All patients with corneal thickness greater than 0.65 mm at discharge were excluded because of suspected endothelial dysfunction.

RESULTS

Of 71 patients studied, 40 measurements from 14 patients were admissible to Group 1 (20 mm Hg difference), and 78 measurements from 39 patients, to Group 2 (10 to 19 mm Hg difference). Two patients who had appropriate pressure ranges were excluded because at discharge they each had a corneal thickness greater than 0.65 mm with suspected endothelial dysfunction.

In the high pressure range of Group 1, the mean pressure with standard deviation was 48.35 ± 15.35 mm Hg, with corneal thickness of .587 ± .078 mm, and in the low pressure range, 21.2 ± 12.2 mm Hg with corneal thickness of .631 ± .084 mm (Table 2). The P value for the corneal thickness difference was .025. Mean pres-

From the Department of Ophthalmology, Louisiana State University School of Medicine, New Orleans, Louisiana. This study was supported in part by Grants EY 00446 and EY 00266 from the National Institutes of Health (Drs. Olson and Kaufman) and a Bausch and Lomb Fellowship (Dr. Olson).

Reprint requests to Randall J. Olson, M.D., LSU Eye Center, 136 S. Roman St., New Orleans, LA 70112.

TABLE 1

GROUP 1 IOP AND CORNEAL THICKNESS MEASUREMENTS TAKEN DURING THE FIRST POSTKERATOPLASTY WEEK

	High Range		Low Range	
Patient	IOP (mm Hg)	Corneal Thickness (mm)	IOP (mm Hg)	Corneal Thickness (mm)
1	32	0.53	10	0.58
	32	0.46	12	0.54
2	22	0.57	2	0.74
3	55	0.69	20	0.72
	35	0.69	15	0.70
4	58	0.62	23	0.64
	50	0.58	22	0.66
	39	0.63	17	0.86
5	54	0.52	32	0.58
6	64	0.60	15	0.64
	58	0.62	34	0.60
7	53	0.52	32	0.62
8	65	0.47	14	0.59
9	28	0.60	6	0.68
10	36	0.57	14	0.62
11	70	0.51	44	0.53
12	66	0.70	34	0.58
	65	0.52	38	0.48
13	58	0.74	35	0.65
14	27	0.61	5	0.62

sure and corneal thickness in Group 2 were 31.1 ± 9.12 mm Hg and .611 ± .089 mm (high pressure range), and 18.0 ± 8.79 mm Hg and .636 ± .096 mm (low pressure range). The P value in comparing corneal thickness in Group 2 was .031. The mean corneal thickness in Groups 1 and 2 combined was .601 ± .085 mm for the high pressure range, and .635 ± .091 mm for the low pressure range, with a P value of .012. All P values were calculated by correlated t-test.

DISCUSSION

Ytteborg and Dohlman[3] showed that in rabbit eyes pressure had little, if any, effect on corneal thickness. The normal, healthy cornea appears to be a relatively closed system, with the epithelium representing a barrier to water diffusion 2.3 times greater than that of the endothelium.[10] Regardless of the pressure in the eye, the closed system would have no pressure gradient across the endothelium and thus, no net water flux. Epithelial edema, on the other hand, would occur when the IOP exceeded the stromal swelling pressure (normally, about −50 to 60 mm Hg[11]) and result in a positive fluid pressure even though the stromal thickness was unchanged. Stromal thickness then would be a function of the pump-leak apparatus and would be affected little, if at all, by IOP.

Ytteborg and Dohlman's[4] clinical work in patients with unilateral glaucoma did not show a significant change in stromal thickness compared to the contralateral normal eye except when pressures were over 40 mm Hg, at which point significant corneal swelling occurred. One pitfall in their study was that many of their patients probably had secondary glaucoma, which would make the health of the endothelium questionable. The higher the pressure, the greater the likelihood of a severe inciting cause, and the greater the possibility of endothelial damage. Marked endothelial loss with trauma, for instance, has been documented.[12]

Ehlers[5,6,8] did not accept the concepts of a negative stromal swelling pressure, the normal cornea as a closed system, or the endothelial pump as a significant factor in corneal deturgescence. He stressed the importance of the mechanical effects of IOP pushing against the endothelium as a limiting membrane. Following this reasoning, one would expect corneal thinning with increased IOP. Work on monkey and rabbit corneas did indeed show a negative stromal-thickness correlation with IOP, but, unfortunately, the epithelium was removed, which destroyed the possibility of a closed system.

Two clinical studies by Ehlers[7] also showed an inverse relationship between pressure and corneal thickness. In his

TABLE 2

RESULTS FOR ALL PATIENTS STUDIED

	Group 1		Group 2		Combined Groups 1 and 2	
	High Pressure Range	Low Pressure Range	High Pressure Range	Low Pressure Range	High Pressure Range	Low Pressure Range
No. of measurements	20	20	39	39	59	59
No. of patients	14	14	29	29	43	43
Mean intraocular pressure with Standard Deviation (mm Hg)	48.4 ±15.4	21.2 ±12.2	31.1 ±9.1	17.7 ±8.6	36.9 ±14.1	18.9 ±10.0
Mean corneal thickness with Standard Deviation (mm)	0.587 ±0.078	0.631 ±0.084	0.611 ±0.089	0.636 ±0.096	0.601 ±0.085	0.635 ±0.091
P value for corneal thickness	.025		.031		.012	

first study, he found that in unilateral retinal detachment with decreased IOP, the affected eye had a cornea significantly thicker than that of the opposite normal eye. One problem with that study is that eyes with retinal detachment may be inflamed, which could conceivably damage the endothelium. The second study was divided into two parts. The first compared corneal thickness in glaucomatous eyes that had not received treatment for several days with that of contralateral control eyes with normal pressures, and no significant thickness differences were found. The second part compared the corneal thicknesses of glaucomatous eyes not receiving treatment and having higher IOPs with the corneal thicknesses of the same eyes after the IOPs were controlled. Those glaucomatous eyes had significantly thinner corneas with increased IOP. The corneal thickness of normal eyes receiving glaucoma treatment with small IOP shifts did not change significantly.

Our study in which each eye served as its own control showed a small but significant amount of thinning with increased IOP. The low pressure reading was generally late in the postoperative course, when the high pressure was controlled, whereas corneal thickness generally decreases spontaneously during that time as the integrity of the endothelial sheet is re-established.[13] That natural tendency for the cornea to thin with time contradicts our observations and thus strengthens the significance of the observed difference.

Corneal thinning with increased IOP could be the result of the endothelial pump being pressure-dependent; however, we presently have no evidence to sup-

port that hypothesis. The pressure could also be acting on the endothelium as a limiting membrane and force the fluid anteriorly. The problem with that theory is that the epithelium is normally 2.3 times less permeable than the endothelium.[10] With increasing pressure, water would be expected to accumulate between two semipermeable membranes in a series in which the second was less permeable than the first and cause swelling. With the epithelial barrier removed, as in Ehlers' experiments, or its permeablility increased beyond that of the endothelium, high IOP would be expected to cause corneal thinning. Possibly, storage of corneas in tissue culture media, the insult of surgery, changes caused by healing, or increased IOP per se can increase epithelial permeability. Obviously, whatever the reason, epithelial permeability must be increased for this corneal thinning to occur.

That high IOP causes increased corneal thickness is a commonly held misconception. On the contrary, it is in eyes with thin, clear corneas after keratoplasty that we have learned to suspect high pressure. The pressure should be checked in the acute postoperative period with an accurate instrument, such as the electronic applanation tonometer.[14]

SUMMARY

We correlated the intraocular pressure readings and measurements of corneal thickness in 71 patients who had had penetrating keratoplasties and found that in the acute post keratoplasty period, increased intraocular pressure caused corneal thinning rather than thickening.

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SERUM OBSTRUCTION OF AQUEOUS OUTFLOW IN ENUCLEATED EYES

DAVID L. EPSTEIN, M.D., JOANN M. HASHIMOTO, B.A.,
AND W. MORTON GRANT, M.D.

Boston, Massachusetts

The mechanism of glaucoma secondary to uveitis has never been clearly established. Possible mechanisms of glaucomatous obstruction to outflow include swelling or dysfunction of trabecular endothelial cells and deposition of inflammatory material in the outflow channels. One of the possible mechanisms in phacolytic glaucoma is the obstruction of the aqueous outflow channels by soluble lens proteins, without intervention of macrophages.[1,2] We investigated the facility of outflow as influenced by human serum proteins, which may leak into the anterior chamber in uveitis.[3]

METHODS

According to a standard technique,[1,4-6] enucleated human eyes were stored at 4° C in a moist chamber and were submitted to quantitative aqueous perfusion within 48 hours after death. A reservoir of perfusion fluid was suspended from a lever arm of an electric force transducer connected to a strip-chart recorder. Calibration measurements established that from the change in weight of the reservoir, the rate of flow could be reliably determined to the nearest 0.1 μl/minute.

In preparation for perfusion, the enucleated eye was allowed to reach room temperature and was gently wrapped in gauze, placed in a plastic cup, and submerged to the corneoscleral limbus in the same physiological salt solution used for perfusion. A 5-mm central corneal trephine button was removed, and a radial iridotomy was performed to prevent artificial deepening of the anterior chamber, which was gently irrigated to remove pigment that might have come loose into the anterior chamber at the time of the iridotomy. A special stainless steel fitting[4] was placed in the cornea and connected to the fluid reservoir of the monitoring apparatus with polyethylene tubing. The cup containing the enucleated eye was placed in a water bath with adjustable temperature. The distance of the eye below the level of the fluid reservoir was varied to establish the desired intraocular pressure. Perfusions were performed at 22° C and 23 mm Hg.

The eyes were first perfused in this manner for an hour to stabilize and provide an initial flow value.[7] Then the corneal fitting was removed, and the anterior chamber evacuated and filled with serum. A corneal fitting was installed, and serum was infused into the anterior chamber from a separate reservoir for 30 minutes at the same pressure as for the initial flow measurements. The corneal fitting was then removed and replaced with the fitting connected to the salt solution reservoir. Flow was again measured by perfusion in the same way as in the beginning. The salt solution used for perfusion was Dulbecco's phosphate-buffered salt solution.

Control eyes were treated in the same way except instead of serum, the salt solution was used in all phases of the experiments.

Serum for the experimental procedures was prepared from blood obtained by venipuncture from normal human volunteers. The blood was allowed to clot at room temperature for 45 minutes, and

From the Howe Laboratory of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts. This study was supported by National Eye Institute Research grants 1 RO1 EY01894 and 5 RO1 EY00002.

Reprint requests to David L. Epstein, M.D., Howe Laboratory, 243 Charles St., Boston, MA 02114.

was then centrifuged at 2,025 × G for ten minutes. The supernatant was passed through a filter sampler, and just before use, the serum was passed through a 1.2-μ Millipore filter.

An Ostwald viscometer measured relative viscosity.

A lens depression perfusion apparatus (Fig. 1), modified from Van Buskirk's,[8] was used to press the crystalline lens posteriorly in a measured, variable, and reversible way to simulate the effect of varying contraction of the ciliary muscle mechanically by increasing and decreasing tension through the zonules and ciliary body on the scleral spur and trabecular meshwork. In experiments involving lens depression, eyes previously perfused quantitatively with salt solution were then perfused for 30 minutes with normal human serum. Then the corneal fitting was replaced with the lens depressor, with the plunger in the neutral zero position, and a repeat perfusion was performed at various settings of the depressor for one hour with salt solution. During lens depression, the plunger was gradually moved to a position 6 mm behind the cornea,[8] and the eye was perfused for one hour with salt solution. Then gradually, the lens depressor plunger was returned to the neutral zero position, in which the plunger and the lens did not touch. Previous experiments have indicated that the lens depression unit in this position does not influence facility of outflow. Similar maneuvers using salt solution instead of serum were performed in control eyes.

In certain experiments attempts were

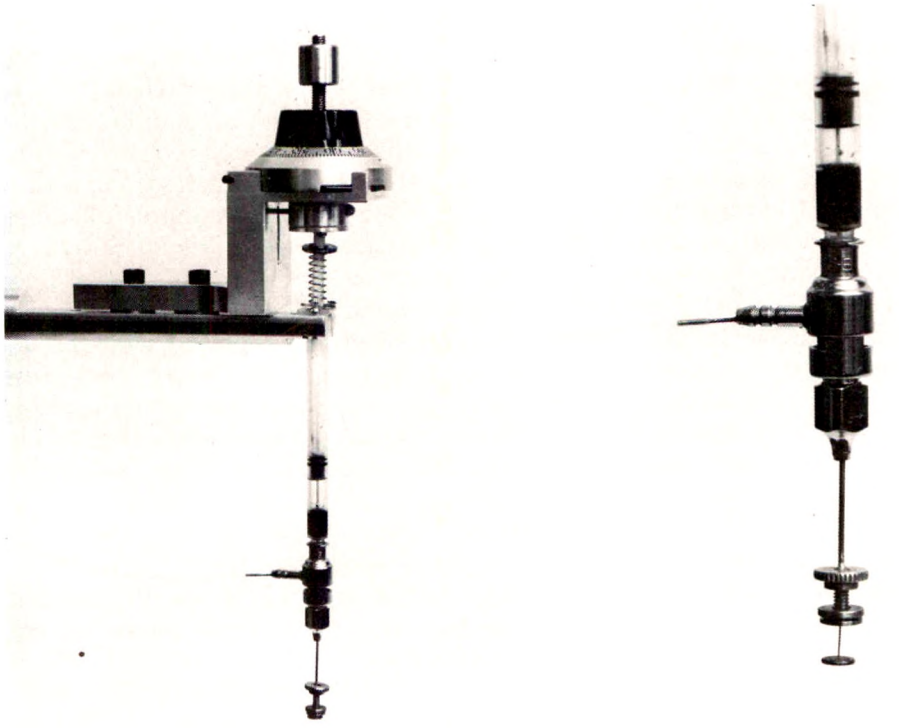


Fig. 1 (Epstein, Hashimoto, and Grant). Lens depression apparatus. The movement of the plunger allows a variably controlled movement of the lens posteriorly. Perfusion fluid flows into the anterior chamber around the plunger through the corneal fitting.

made to wash out the anterior chamber by removing the corneal fitting and irrigating the anterior chamber with 5 ml of balanced salt solution or 1:5000 alpha-chymotrypsin.

RESULTS

Infusion of normal human serum into enucleated human eyes for 30 minutes induced a 42% decrease in facility of outflow (Fig. 2). The obstruction of aqueous outflow was not relieved by irrigation of the anterior chamber with balanced salt solution or alpha-chymotrypsin (Fig. 2).

The influence of various dilutions of human serum on outflow appears in Figure 3. A serum dilution of 0.25 (that is, 25% serum and 75% salt solution) decreased the facility of outflow by 36% (Fig. 3). The obstruction of outflow induced by serum diluted to 0.25 and 0.50 did not differ from that induced by whole serum as significantly as might be expected on the basis of measured difference in viscosity.

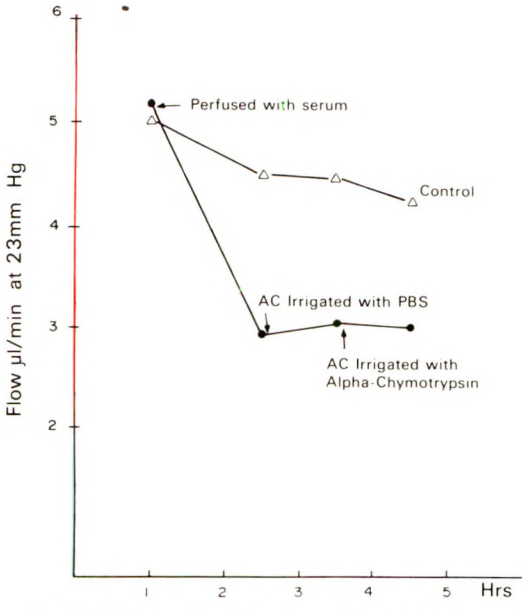


Fig. 2 (Epstein, Hashimoto, and Grant). Effect of normal human serum on fluid outflow. Serum was perfused into the experimental eyes for 30 minutes following a preliminary one-hour aqueous perfusion and measurement of outflow (arrow). Results are shown for 38 serum-treated eyes (solid circles) and 24 sham-treated controls (open triangles). Attempts were made to reverse the effect by washing out the anterior chamber, (seven eyes) (AC designates anterior chamber; PBS, phosphate-buffered salt solution).

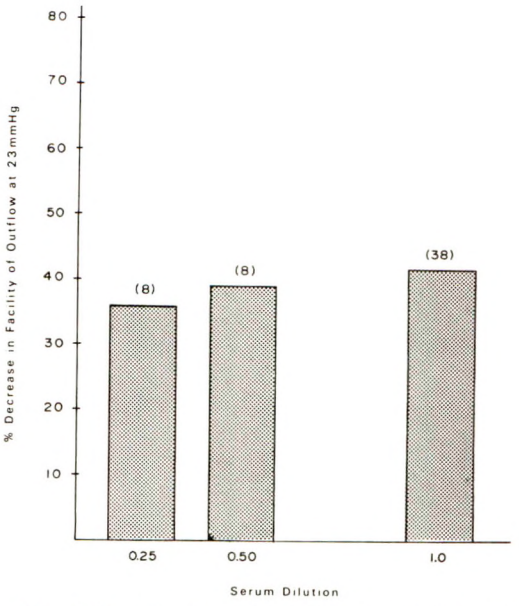


Fig. 3 (Epstein, Hashimoto, and Grant). Effect of different dilutions of normal human serum on fluid outflow. The number of eyes in each group is shown in parentheses.

Lens depression increased the total outflow facility in eyes previously perfused with serum (Fig. 4). However, the obstruction of outflow induced by serum

TABLE

EFFECT OF SERUM DILUTION ON OUTFLOW FACILITY

Serum Dilution	Relative Viscosity	Δ Expected*	Δ Observed
0.25	1.12	−11%	−36%
0.50	1.29	−22%	−40%
1.00	1.70	−41%	−42%

*The percent Δ expected = $100 - \frac{1}{\text{relative viscosity.}}$

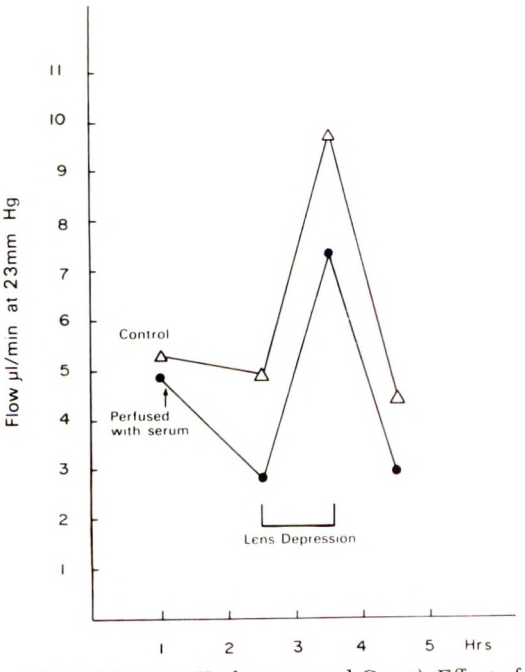


Fig. 4 (Epstein, Hashimoto, and Grant). Effect of lens depression on serum outflow obstruction. Serum was perfused for 30 minutes into the experimental eyes as in Figure 2. After one hour of subsequent perfusion with phosphate-buffered salt, 6 mm of lens depression was produced, followed by return of the plunger to the neutral position. Results from seven pairs of eyes are shown (serum-treated, solid circles; sham-treated controls, open triangles).

persisted after the eye was subjected to variable lens depression (Fig. 4).

Discussion

The effect of uveitis on the aqueous outflow channels may be masked by associated hyposecretion of aqueous humor, and the intraocular pressure may vary, depending on the predominance of outflow obstruction or hyposecretion. To avoid the problem of aqueous formation, we studied the effects of serum on the outflow facility in freshly enucleated eyes, which are free from neurogenic and vascular impulses. Obstruction to outflow in uveitis is no different after death than in life. Perfusion of an eye from a patient with uveitis demonstrated postmortem impairment of outflow facility.[9]

Infusion of human serum into the anterior chamber of enucleated human eyes for 30 minutes results in a significant reduction in outflow facility (Fig. 2). Many years ago Troncoso[10] reported a similar result. The obstruction is less than that produced by lens proteins,[1] presumably because of the lower molecular weight of serum proteins, but the obstruction to outflow was sufficient to be a potentially influential factor in glaucoma secondary to uveitis. Excess serum proteins may have particular influence in the aqueous humor of eyes with quiescent uveitis, with little residual cellular reaction but persistent anterior chamber flare and glaucoma refractory to corticosteroid therapy.

A protein concentration in the aqueous humor as high as 1.3 g/100 ml (approximately 0.25 dilution of serum) has occurred in patients with uveitis.[3] In our studies this concentration significantly impaired outflow facility (Fig. 3). The obstruction to outflow at the lower serum dilutions is greater than expected from viscosity measurements on the diluted serum, as compared to the full strength serum (Table). Therefore, the proteins may actually interfere with outflow in a more complex way than through abnormal viscosity.

Irrigation of the anterior chamber fails to relieve the obstruction of outflow by serum (Fig. 2). Tension on the iridocorneal angle induced by lens depression, to simulate ciliary muscle contraction,[8] does produce a conspicuous improvement in outflow facility, but a difference persisted in facility of outflow between control eyes and those previously perfused with serum (Fig. 4). Perfusion with protein-free salt solution with tension on the iridocorneal angle induced by lens depression does not dispel the obstructive effect of serum better than simple salt-solution perfusion,

which suggests that serum may be deposited in or adsorbed to the trabecular meshwork. Serum seems to be resistant to being washed out through the outflow channels. The results of the lens depression suggest that if obstruction of outflow by serum proteins is involved in persistent secondary glaucoma in quiescent uveitis, miotics may improve outflow facility and intraocular pressure, but not cure the glaucoma.

Summary

We perfused enucleated human eyes via the anterior chamber by the constant pressure technique. Infusion of human serum into the anterior chamber of enucleated human eyes for 30 minutes at 23 mm Hg pressure induced a 42% decrease in facility of outflow, which was not relieved by irrigation of the anterior chamber with balanced salt solution or alpha-chymotrypsin. Diluted serum also reduced the facility of outflow. Measured in a glass viscometer, diluted serum had less viscosity than undiluted, but interfered with outflow from the eye more than anticipated on the basis of viscosity alone.

When we used lens depression to induce tension on the iridocorneal angle to simulate the effects of contraction of the ciliary muscle, outflow facility increased in control eyes that had not been exposed to serum and in serum-perfused eyes. However, the partial obstruction to outflow that had been induced by serum persisted.

Normal serum components may become adsorbed or entrapped in the aqueous outflow system so as to obstruct outflow, and this may result in secondary glaucoma in eyes with chronic uveitis.

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SUBACUTE SCLEROSING PANENCEPHALITIS

RICHARD F. GRAVINA, M.D., ALAN S. NAKANISHI, M.D., AND ALAN FADEN, M.D.

San Francisco, California

Subacute sclerosing panencephalitis is a progressive neurologic disease affecting children and young adults. The mean age of onset is about seven years, and males are affected approximately three times more frequently than females.[1] Subacute sclerosing panencephalitis usually begins with personality or behavioral changes, followed over a variable period by dementia, seizures, myoclonus, and, eventually, death. Although subacute sclerosing panencephalitis classically has a clinical course of several months to several years, a number of reports have documented a relatively prolonged course, occasionally with remission and exacerbations.[2–5]

There is a high incidence of visual system abnormalities that occur during the course of the illness and that may occur before the central nervous system manifestations.[6,7] We report herein a patient, however, in whom the ophthalmologic complications antedated the central nervous system manifestations by 22 months, an unprecedently long time.

CASE REPORT

A 17-year-old white woman came to our clinic in November 1969 with a painless loss of vision in her left eye. This occurred over three days without other symptoms. She had had rubeola at the age of 3 years and had attained normal development and educational milestones. On ophthalmogic examination, visual acuity was R.E.: 6/6 (20/20), J1; L.E.: 6/60 (20/200), J12. The cornea, anterior chambers, lenses, and vitreous bodies were normal. Ophthalmoscopic examination revealed no abnormalities in the right eye except for numerous flecklike spots near the ora serrata between the 5 and 8 o'clock positions. The left eye had slight elevation of the disk along its temporal margin, moderate macular edema, and two small areas of intraretinal hemorrage above and below the fovea (Fig. 1). Hruby lens examination showed the right eye to be normal, but in the left, the entire macula and much of the surrounding posterior pole were raised and edematous. The left fovea and the area one disk diameter temporal to the fovea appeared cystic. Fluorescein angioscopy showed hyperfluorescence in the cystic areas, maximally ten minutes after injection of the dye. No staining was noted after 60 minutes.

We made no definite diagnosis at this point and examined the patient at regular intervals over the subsequent four months. Her general health and visual acuity remained stable; the hemorrhage and edema had resolved somewhat (Fig. 2). The cystic lesions of the left eye were photocoagulated in March 1970 (Fig. 3). She remained well until September 1971, when she noted difficulty in her left visual field. Ophthalmologic examination then demonstrated a left homonymous hemianopia. In addition to the old photocoagulation scars, several fine, gray-white atrophic areas appeared in the perimacular region of the left fundus. The right fundus was unchanged. The patient was admitted to the University of California Medical Center, San Francisco, where the only neurologic abnormalities diagnosed were a marked constructional apraxia and the visual



Fig. 1 (Gravina, Nakanishi, and Faden). Left eye. Areas of intraretinal hemorrhage are present around the fovea and one disk diameter temporal to the fovea. The macula is edematous.

From the Department of Neurology, University of Caifornia, San Francisco, California (Drs. Gravina and Faden) and the Department of Ophthalmology, Pacific Medical Center, San Francisco, California (Dr. Nakanishi).

Reprint requests to Richard F. Gravina, M.D., 101 South San Mateo Drive No. 201, San Mateo, CA 94401.

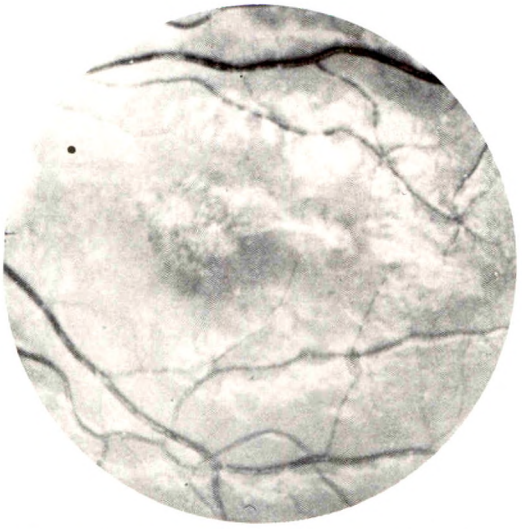


Fig. 2 (Gravina, Nakanishi, and Faden). Left eye. One month later, the intraretinal hemorrhages and macular edema are less prominent.

field defect. Bedside tests of mental status gave normal results. Complete blood cell count, urinalysis, routine chemistries, serum VDRL, antinuclear antibody, rheumatoid factor, and radiographs of the skull and chest were normal. The sedimentation rate was increased to 36 mm/hr. Serum protein electrophoresis revealed an increased gamma globulin of 1.7 g/100 ml (upper limit of normal, 1.4 g/100 ml). A lumbar puncture revealed an opening pressure of 120 mm/H_2O, and the spinal fluid contained 3 lymphocytes per cubic millimeter, a protein of 38 mg/100 ml, and a blood glucose of 59 mg/100 ml. Spinal fluid VDRL and India ink preparations were negative, as were spinal fluid cultures for bacteria, acid-fast bacillus, and fungi. A brain scan was equivocally positive in the right parietal area. Bilateral carotid and vertebral angiography were normal. She was discharged with a diagnosis of a right parietal lobe infarction of unknown cause.



Fig. 3 (Gravina, Nakanishi, and Faden). Left eye. Four months after onset of visual symptoms, the intraretinal hemorrhages are less apparent, and two photocoagulation scars temporal to the fovea are present.

From December 1971 to August 1972, she experienced progressive deterioration in memory and attentiveness, and episodic confusion. She was readmitted to the hospital in August 1972 (aged 19 years), and neurologic examination revealed poor short-term memory, difficulty in performing the serial sevens test, inability to add two-digit numbers, and severe constructional apraxia. The rest of the neurologic examination, including the visual field examination, was normal. Visual acuity was R.E.: 6/6 (20/20); L.E.: 6/60 (20/200). The ophthalmoscopic appearance of the eyes had not changed. Psychometric evaluation demonstrated a verbal intelligence quotient of 88, a visual motor score of 52, and a memory intelligence quotient of 69. Brain scan was normal. Bitemporal slowing in the range of 3 to 4 Hz appeared on the electroencephalogram. A pneumoencephalogram showed minimal dilation of the lateral ventricles. Lumbar puncture revealed an opening pressure of 130 mm/H_2O, 0 leukocytes per cubic millimeter, 140 erythrocyes per cubic millimeter, protein of 29 mg/100 ml, glucose of 60 mg/100 ml, and gamma globulin of 33%. Spinal fluid VDRL and fluorescent treponemal antibody were negative. Serum antibodies to mumps, herpes simplex, St. Louis, Venezuelan, and Western equine viruses were 1:8; measles was 1:512 (normal<1:8). Complement fixation antibodies to mumps and herpes simplex were 1:2, and measles 1:16 (normal <1:8). The increased spinal fluid gamma globulin was confirmed on a subsequent lumbar puncture (31%). We made a tentative diagnosis of subacute sclerosing panencephalitis and discharged the patient.

On readmission in September 1973, the patient showed progression of dementia. The only neurologic abnormalities were a mild symmetrical hyperreflexia and multifocal myoclonic jerking of the fingers. Visual acuity was R.E.: 6/15 (20/50); L.E.: 6/30 (20/100). No Marcus Gunn pupil was noted. The previously noted peripheral lesions of the right eye had increased slightly. The right macula and optic nerve appeared normal, and the left fundus remained unchanged. Psychometric testing revealed a global deterioration in all aspects. A lumbar puncture showed an opening pressure of 160 mm/H_2O, 1 lymphocyte per cubic millimeter, protein of 38 mg/100 ml, and a gamma globulin of 30%. Serum and spinal fluid measles titers were 1:512 and 1:32, respectively. The electroencephalogram showed bursts of high-amplitude sharply contoured, slow

wave complexes, which were considered to be pathognomonic for subacute sclerosing panencephalitis.

Discussion

During the course of their illness, approximately 50% of patients with subacute sclerosing panencephalitis manifest visual system abnormalites,[6] which include focal chorioretinitis, visual field defects, optic atrophy, cortical blindness, and nystagmus.[7-10] The majority of the defects involve the retina, either in the macular or perimacular region.[8] Such findings may suggest primary intraocular disease, such as nonspecific chorioretinitis or juvenile macular degeneration, and are bilateral in only 30% of the cases.[10] Since the early brain parenchymal process is thought to affect the occipital areas and then extend anteriorly,[11] early crebral visual abnormalities may also occur.

There is a high correlation of subacute sclerosing panencephalitis with a preceding rubeola infection, which usually occurs before 2 years of age.[1] Moreover, it has been repeatedly demonstrated by electron microscopy and immunofluorescent techniques that the intranuclear inclusion bodies seen in the brain parenchyma in subacute sclerosing panencephalitis contain measles virus. By light microscopy, the intranuclear inclusions (Cowdry type A) have been found in retinal cells[7] and the optic nerves[12] in patients with subacute sclerosing panencephalitis. Electron microscopic studies of retinal cells have shown microtubules consistent with viral nuclear capsids identical to those observed in brain tissue.[12,13] Immunofluorescent techniques have shown that the infected retinal cells are positive for measles antigen.[14]

Although the maculopathy of subacute sclerosing panencephalitis may precede the neurologic syndrome, the neurologic abnormalitites usually follow the ophthalmologic findings in several weeks to several months. In two cases, however, a maculopathy occurred six months before the development of neurologic symptoms.[10,14] In a third case, the maculopathy antedated other signs and symptoms by eight months.[6] Our study indicates that the retinal manifestations of subacute sclerosing panencephalitis may precede the neurologic abnormalities by an even longer period.

In view of the protean retinal abnormalities in subacute sclerosing panencephalitis, the possibility of the disease should be considered in children or young adults who have a maculopathy of unknown etiology. In addition to a neurologic examination, two diagnostic studies that should be considered in examining such patients are serum measles titers and psychometric examination. The latter may demonstrate early signs, not otherwise apparent, of a deteriorating mental state.

Summary

A 17-year-old white woman had an acute left maculopathy of unknown etiology. She was in excellent health and had only had rubeola at 3 years of age. Hruby lens examination of the left eye, visual acuity of 6/60 (20/200), revealed a normal vitreous, macular edema, intraretinal hemorrhage, and cotton-wool exudates. Xenon photo-coagulation was performed on the left eye. The visual acuity remained 6/60 (20/200) with drying of the retina. The patient remained in excellent health until 22 months after the initial ocular problem when she developed a left homonymous hemianopia. Then her mind deteriorated, and she became demented. We diagnosed subacute sclerosing panencephalitis after finding an increased spinal fluid gamma globulin, raised serum and spinal fluid titers of measles antibodies, and an electroencephalogram pathognomonic for this condition.

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OCULAR CRYPTOCOCCOSIS

JOSÉ AVENDAÑO, M.D., TERUO TANISHIMA, M.D., AND TOICHIRO KUWABARA, M.D.
Bethesda, Maryland

Because of extensive therapeutic usage of cytotoxic, antibiotic, and corticosteroid drugs in recent years, intraocular fungus infection has significantly increased in patients who have neoplastic malignancies and have undergone chemotherapy.[1] *Cryptococcus* is one of several fungi commonly found in the environment. *Cryptococcus neoformans* (*Torula histolytica*) is a round yeast found in soil, dry stools of many animals, fruits, and cows' milk.

With light and electron microscopy, we examined the eye of a patient who had developed generalized cryptococcosis after extensive treatment of a diffuse histiocytic malignant lymphoma of the abdomen.

CASE REPORT

A 59-year-old man was found to have a malignant histiocytic lymphoma in the lower abdomen by exploratory laparotomy and histologic examination in June 1976. He received treatment with radiation and cyclophosphamide, vincristine, procarbazine, and prednisone.

The patient complained of diplopia one month after hospitalization. An ophthalmic examination revealed that the left eye had moderate orbital infiltration and retinal folds, presumably because of lymphoma. After two months of complications including pancytopenia and herpetic eruption, the patient died on Nov. 18, 1976. Blood culture and skin biopsy done shortly before death showed a growth of *Cryptococcus*.

The autopsy revealed widespread malignant lymphoma and foci of cryptococcal infection in various organs.

RESULTS

Opening the eyes, we discovered a few small hemorrhagic lesions and small yellowish-white spots in both retinas. No abnormality was found by gross examination except for peripheral cystic changes. However, close examination revealed that several small lesions with thickened choroidal tissue and grayish mucinous substances were present on the cut surface of the posterior choroid of both eyes.

Histologic sections revealed extensive infection of the posterior choroid by *C. neoformans*. The organisms were PAS-positive spherical particles of about 5 μ in diameter and surrounded by a thick mantle of mucopolysaccharide (Fig. 1). A portion of the mantle took a deep alcian blue stain. The fungus was abundantly present in the choriocapillaris and in the deep choroidal tissue and sometimes formed intravascular clusters. Several large nodular foci of infection appeared edematous because of accumulation of the mucinous substance. Except for a sparse neoplastic (lymphocytic) infiltration, no inflammatory reaction appeared in the infected choroid or other parts of the eye. Bruch's membrane was intact, and the subretinal space and retina were fungus-free. The overlying retina appeared normal. Other ocular abnormalities were moderate cys-



Fig. 1. (Avendaño, Tanishima, and Kuwabara). *Cryptococcus neoformans* in the choroid. Bruch's membrane and retinal pigment epithelium are intact (PAS, ×500).

From the Clinical Branch and Laboratory of Vision Research, National Eye Institute, National Institutes of Health, Bethesda, Maryland.

Reprint requests to Toichiro Kuwabara, M.D., Building 6, Room 213, National Institutes of Health, Bethesda, MD 20014.

tic change in the peripheral retina, mild vacuolation of the cortical lens fibers, and marked hyalinalization of the ciliary process.

Small pieces of the formalin-fixed choroid of the right eye were excised and postfixed in 1% osmium tetroxide for one hour. The tissue was dehydrated in alcohol and embedded in epoxy resin. Ultrathin sections were stained with lead citrate and uranium acetate, and examined by electron microscopy. Most of the yeast bodies were spherical with small protrusions (Figs. 2 and 3). The protrusion was apparently a portion of a bud of the fungus. A thick capsule consisting of lamellar basal lamina-like substances of uniform thickness (0.25 μ) encased the fungus cell body. The cell had a small nucleus and a moderately electron-dense granular cytoplasm with a few mitochondria, vacuoles, and rough-surfaced endoplasmic reticulum. The fungi, including the capsule, were approximately 4 to 5 μ in diameter. Outside the organism was a large area of a finely filamentous amorphous substance that formed a coating about 1 μ thick and gradually dispersed into the tissue space. The substance corresponded to the area that showed an alcian blue stain. A minute space appeared between the capsule and mucopolysaccharide coating (Fig. 3).

The fungi occurred mainly in the extracellular space, but also inside certain cells, perhaps histiocytes. The intracellular fungi were degenerating and irregular in shape, size, and density. Histiocytes often contained lipid droplets and other inclusion bodies (Fig. 4). No hyphae form

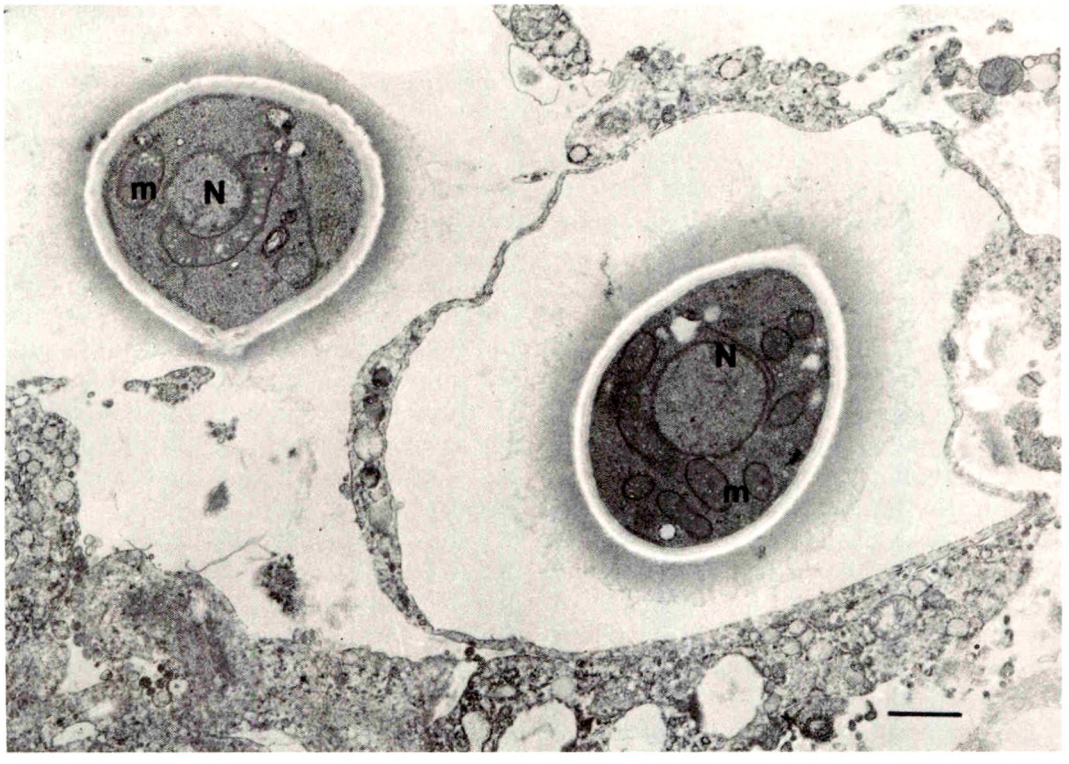


Fig. 2. (Avendaño, Tanishima, and Kuwabara). Electron micrograph of a portion of the infected choroid. The cryptococci are surrounded by fine cell processes. The fungus contains a small nucleus (N), mitochondria (m), and rough endoplasmic reticulum (bar gauge = 1 μ) (×9,200).

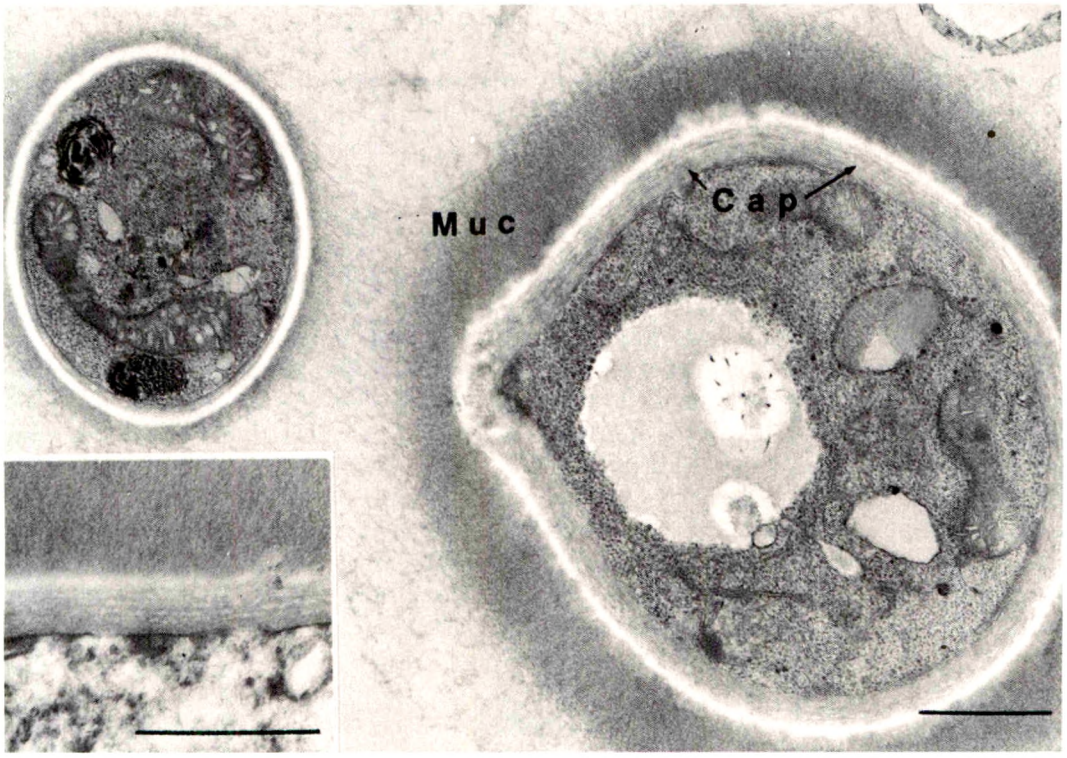


Fig. 3. (Avendaño, Tanishima, and Kuwabara). The fungus has a thick capsule (Cap) and a coating of mucopolysaccharide (Muc) (bar gauge = 1 μ) (×17,000).

of the fungus appeared in the choroid, and no other organisms were found in the eyes.

Discussion

The site of entry and the most common organ infected with *Cryptococcus* is the lung. Cryptococcal meningitis, which causes visual dysfunction, is one significant ophthalmic manifestation of the infection. Kupfer and McCrane[2] described six such cases of involvement of the fungal infection in the visual tract. Hiles and Font[3] and Khodadoust[4] reported cases of cryptoçoccal retinitis. The hemorrhagic lesions and the whitish spot in the retina in our case did not contain the fungus.

Cryptococcal infection characteristically causes little necrosis or cellular reaction. However, Zimmerman and Rappaport[5] and Littman[6] observed a granulomatous reaction in the infected tissue. Although they noted phagocytosis of fungi in histiocytes, no granulomatous changes occurred in this case. The total absence of cellular reaction indicates that chemotherapeutic drugs generally suppress the host cells. Additionally, because of the rapid progress of the lymphoma, the time is probably insufficient for the reaction to occur before the death of the patient.

Peterson, Hawley, and Calderone,[7] and Kwon-Chung and Pepkin[8] and others reported electron microscopic studies of the fungus. Our findings are compatible with these earlier results. However, most of the previous studies dealt with cultured pure samples, and not with an infected lesion. The *Cryptococcus* in our study showed a large amount of mucin substances, which had not been reported in previous studies.

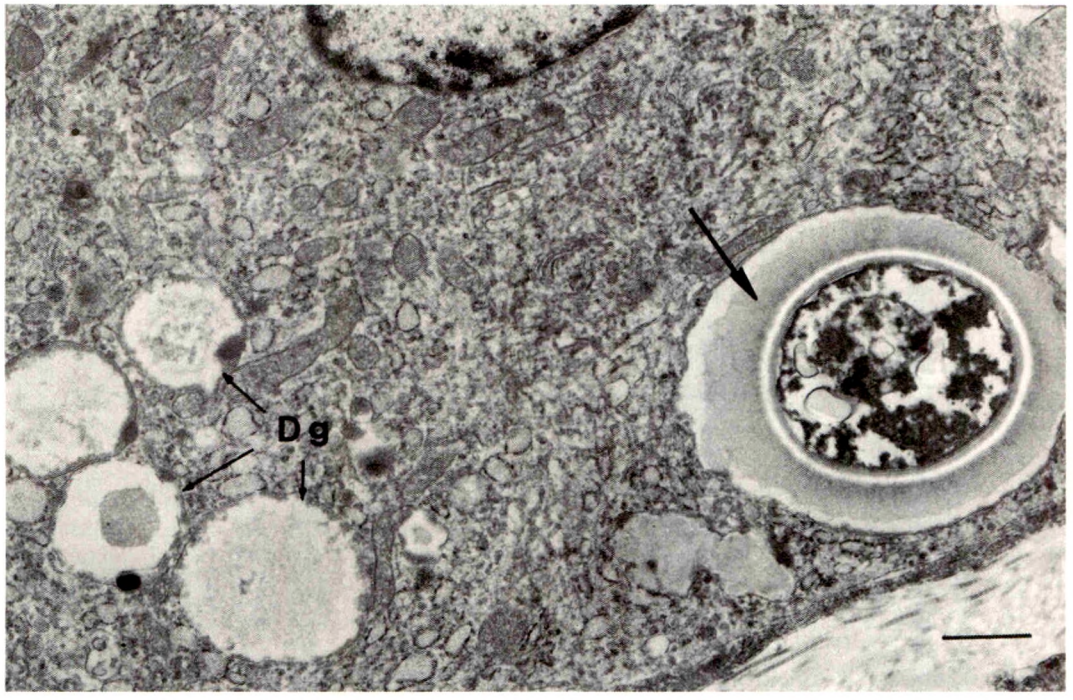


Fig. 4. (Avendaño, Tanishima, and Kuwabara). A portion of a histiocyte containing degenerating fungi (Dg). The arrow indicates condensed mucous material (bar gauge = 1 μ) (×11,500).

Although the exact site of production is not clear, the mucin is apparently a product of the organism, perhaps coming from the capsule through dispersion of its substance. The mucinous substance seems to isolate the fungus from the surrounding tissue.

Summary

We studied ocular cryptococcosis in a 59-year-old man who had received extensive chemotherapy for abdominal malignant lymphoma. Mucinous lesions containing abundant cryptococci, but no inflammatory cells, formed in the posterior choroid of the eye. Electron microscopy revealed that mucin, a filamentous substance, coated the encapsulated organisms. Except for a few degenerating ones in histiocytes, most cryptococci appeared in the extracellular space.

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HORNER'S SYNDROME WITH IPSILATERAL ACCOMMODATIVE PARESIS

LARRY WEISFELD, M.D., AND BARBARA W. STREETEN, M.D.

Syracuse, New York

The association of Horner's syndrome and accommodative abnormalities is a well described entity. Cobb and Hunter[1] showed the near point of accomodation to be 1 to 4 cm closer on the side of the Horner's syndrome. In five patients with Horner's syndrome, Cogan[2] described an increase in near accommodation, and in one patient, a decreased ability to change from near to far fixation on the side of the Horner's syndrome, which he suggested was a paresis of accommodation for distance. Glaser[3] presumably refers to this patient when he speaks of the "defective accommodation" in patients with Horner's syndrome. In their analysis of 216 cases of Horner's syndrome, Giles and Henderson[4] also noted the association of an increase in the amplitude of accommodation for near on the side of the Horner's syndrome.

We describe herein a case of a Horner's syndrome with an accommodative paresis for near.

CASE REPORT

A 12-year old girl came to our office in January 1977 complaining of a right "droopy" eyelid, which, approximately one month before examination, the mother first noticed to be more apparent at certain times than at others. Pictures of the patient at $10\frac{1}{2}$ years of age failed to reveal any eyelid abnormalities. She had no history of pruritis, redness, trauma, ocular disease, or surgery. The patient also complained that recently letters were transiently "blurry" when she read with her right eye. She denied diplopia, headache, tinnitus, vertigo, paresthesias, extremity weakness, cough, chest pain, and urinary abnormalities.

In the summer of 1975 the patient developed episodes of rhinorrhea and wheezing. An allergist found her to have dust-ragweed allergy and began giving her desensitization shots in January 1976, which have been continued to the present. She used diphenhydramine pseudoephedrine as needed. Her past medical history was otherwise unremarkable.

Family history was remarkable in that the mother was born with a droopy left eyelid. Ocular examination of the mother revealed 2 mm of left blepharoptosis, but no pupillary abnormalities, with or without cocaine drop testing.

Results of physical examination by the Pediatric and Pediatric Neurology services were within normal limits except for the ocular findings.

Ocular examination revealed an uncorrected visual acuity of R.E.: 6/7.5 (20/25) and J-2 at 50 cm; L.E.: 6/6 (20/20) at distance and J-1 at 33 cm. The near point of accommodation was tested by presenting a Lebensohn Near Vision chart at a distance at which the patient could easily read the Jaeger 2 line. The chart was gradually moved closer to the point at which the patient could no longer read the Jaeger 2 line. The chart was then gradually moved away from the patient and the point at which she could easily read the Jaeger 2 line was measured in centimeters from the lateral orbital rim of the eye being tested and recorded as the near point of accommodation, which was 48 cm for the right eye and 7 cm for the left eye. We repeated the measurements many times and tested improvement of the near point of accommodation with plus lenses and ability to overcome minus lenses at a distance. All measurements consistently showed the same degree of asymmetry of the accommodative amplitude for near. Cycloplegic refraction with 1% cyclopentolate was R.E.: +1.50 sph. = 6/6 (20/20); L.E.: +2.00 sph. = 6/6 (20/20). Extraocular motions were full, and the patient was orthophoric at distance and near.

The right upper eyelid had 3 mm of blepharoptosis with excellent levator function; the left eyelid was normal. There was no Cogan's (eyelid twitch) sign, and the blepharoptosis was not exaggerated on prolonged upgaze. The blepharoptosis did not improve with $\frac{1}{8}$% topical epinephrine. Eversion of both eyelids did not reveal any disease. Hertel exophthalmometer reading, base 86, showed R.E.: 14; L.E.: 13. The right pupil measured 3 mm, the left pupil 5 mm. This 2 mm of anisocoria did not change in dim light, but lessened in bright light. Each pupil was circular and reacted briskly to light, directly and consensually, and to convergence. Slit-lamp examination of the conjunctiva, cornea, anterior chamber, and lens was within normal limits. The irises were brownish-green and showed no atrophy. Intraocular pressure measured by applanation tonometry was R.E.: 12 mm Hg; L.E.: 12 mm Hg. Opthalmoscopic examination showed the optic nerves to be sharp, pink, and with a cup:disk ratio of 0.1 in each eye. The macular regions were within

From the Department of Ophthalmology, State University of New York, Upstate Medical Center, Syracuse, New York.

Reprint requests to Larry Weisfeld, M.D., Department of Ophthalmology, State University of New York Upstate Medical Center, 750 East Adams St., Syracuse, NY 13210.

normal limits in both eyes, and the fundus periphery was normal with indirect ophthalmoscopy. Visual field examination by tangent screen, with a 2-mm white test object at 1 meter, was full to 35 degrees in each eye.

Several drug tests were performed on separate days. Two drops of 4% cocaine in each eye at 40 minutes produced full dilation of the left pupil, but none in the right pupil. Two drops of 1% hydroxyamphetamine in each eye produced at 40 minutes full pupillary dilation in each eye.

In February 1977 (one month later), the patient was admitted to the hospital for further diagnostic studies. Skull, chest, and cervical spine x-ray films were reported as negative. A computed tomographic scan of the skull and brain showed poorly identified suprasellar cisterns, which the radiologist thought to be normal. Since a contrast study was not done because of the patient's allergic manifestations to the dye, the radiologist did not want to dismiss the possibility of a small lesion. A starch iodide sweat test proved inconclusive. Results of complete ear, nose, and throat examination by an otolaryngologist were within normal limits. Laboratory examination showed: white blood cell count: 8,100 mm^3; hematocrit, 37.1%; bands, 2%; neutrophils, 62%; eosinphils: 15%; lymphocytes, 13%; monocytes, 8%. The patient's eosinophils, according to her allergist, was consistent with her disease process. A urinalysis and 24-hour urine catecholamines were within normal limits. The zeta sedimentation rate was 46, and the VDRL was nonreactive. Rheumatoid factor and antinuclear antibody titer were negative.

In June 1977 (six months after initial examination), the patient's condition had not changed. She was given 8 mg of edrophonium chloride intravenously: 2 mg slowly over 30 seconds, and the remaining 6 mg 15 seconds later (the patient's weight was 44 kg). The patient experienced some abdominal cramps and diaphoresis. Her blepharoptosis and anisocoria did not change, but her near point of accommodation measurements did (for five minutes): in the right eye, a 40-cm near point of accommodation changed to 10 cm; and in the left eye, it changed from 6 cm to 4 cm.

When the patient returned in October 1977 (ten months after initial examination), the mother reported that the right eyelid had once drooped so completely that the patient "could not see at all." Over a period of three hours the eyelid had gradually returned to its usual level. The mother also claimed that the patient had had intermittent periods of "weakness," but generally was active and performed well in gym at school. Examination at this time revealed the blepharoptosis and anisocoria to be unchanged, but the near point of accommodation measurements were 23 cm in the right eye and 6 cm in the left. The patient was able to hold both arms over her head for 1½ minutes with extreme effort. Eight milligrams of edrophonium chloride was given exactly as described before, and the resultant near point of accommodation measurements were 8 cm in the right eye, and the left showed no change. After administration of the drug, the patient was able to hold up her arms for more than four minutes. An electromyogram of the proximal arm musculature performed by a neurologist three weeks later was normal. An edrophonium chloride test administered one month later by a pediatric neurologist was negative.

When the patient returned two months later, her visual acuity was 6/6 (20/20) in each eye with a plano manifest refraction. Near point of accommodation measurements were 30 cm in the right eye and 8 cm in the left. The blepharoptosis and anisocoria were unchanged. We tried to demonstrate induced astigmatism with accommodation by refracting each eye while the patient fixated at a distance through a −2 lens. No induced astigmatism was noted in either eye. Tonicity of accommodation was checked in each eye separately by having the patient fixate the Jaeger 2 line at a distance of 33 cm for ten seconds. The time in which the 6/6 (20/20) distance line could then be read was recorded. The right eye measured 10 seconds, the left eye, 2 seconds. To demonstrate supersensitivity of the ciliary muscle, we put two drops of 0.25% pilocarpine in each eye and tested the subjective refraction every five minutes for the next hour. The end point of each refraction was the least minus or most plus needed to read the 6/6 (20/20) line. An induced myopia occurred in each eye, maximal at 40 minutes, when the right eye measured -1.75 sph., the left eye, -0.50 sph. Near point of accommodation measurements without correction at this point showed R.E.: 23 cm; L.E.: 8 cm. Both pupils constricted to 2 mm at 40 minutes. The patient was checked for signs of systemic autonomic neuropathy. She did not demonstrate orthostatic hypotension, and normal slight slowing of the pulse occurred in response to Valsalva's maneuver.

DISCUSSION

The diagnosis of Horner's syndrome in this patient is based on the blepharoptosis, the ipsilateral miosis, and the failure of the miotic pupil to respond to 4% cocaine, whereas the opposite pupil dilated widely. The dilation of the pupil after administration of 1% hydroxyamphetamine suggested a preganglionic lesion.[5] The history of recent onset and lack of abnormalities on past photographs suggested that the Horner's syndrome had been acquired. Causes of acquired Horner's syndrome have been well documented,[4] but despite exhaustive examination of this patient, we found no distinct cause.

Based on successive near point of accommodation measurements, we established that the patient had a right-sided

accommodative paresis for near, associated with the ipsilateral Horner's syndrome. Before this case, the only accommodative changes associated with Horner's syndrome were an increase in the accommodative amplitude for near (as determined by a smaller near point of accommodation on the side of the Horner's syndrome) and a decrease in accommodation for distance as described by Cogan.[2]

Although none of the well-recognized causes of accommodative paresis[6] could explain this problem, we explored two possibilities in this patient. First, the improvement in the accommodative paresis after intravenous administration of edrophonium chloride suggested the diagnosis of myasthenia gravis. Manson and Stern[7] reported an increase in the near point of accommodation between 8 and 15 cm with intravenous edrophonium chloride in five patients with generalized myasthenia gravis and in three patients with ocular myasthenia. As his initial manifestation of myasthenia gravis, one of these patients developed difficulty with near accommodation. Intravenous administration of edrophonium chloride did not change the near point of accommodation in 17 controls, although it did significantly change it in 11 patients with nonspecific accommodative problems.

Corroborations of the diagnosis of myasthenia gravis in our patient are: (1) the response of the accommodative paresis to intravenous edrophonium chloride, which was consistent with the findings of Manson and Stern[7] in myasthenia; (2) the history of complete blepharoptosis of the right eyelid on one occasion; and (3) one positive edrophonium chloride test for upper extremity strength. However, the diagnosis of myasthenia gravis is by no means definitive considering that (1) Manson and Stern's[7] findings were not specific for myasthenia gravis, (2) the electromyogram was normal, and (3) the positive edrophonium chloride test for muscle strength could not be duplicated.

We know of no association between myasthenia gravis and Horner's syndrome. A thymoma, a well-recognized entity associated with myasthenia gravis, could conceivable produce a Horner's syndrome. No evidence for such a tumor has been found as yet.

Another possibility besides myasthenia is that our patient had a "pupil-sparing Adie's syndrome." Bell and Thompson[8] mentioned a pupil-sparing Adie's syndrome to explain the findings in two patients who had a classic Adie's syndrome on one side and later developed strictly accommodative abnormalities in the other eye. Although our patient's pupil demonstrated none of the findings of the tonic pupil,[9] her accommodative paresis showed many characteristics of Adie's syndrome,[8] such as: (1) improvement in the paresis with time, (2) tonicity of accommodation, and (3) supersensitivity of the ciliary muscle to 0.25% pilocarpine. Induced astigmatism with accommodative effort, which often occurs in Adie's syndrome,[8] was not demonstrable in our patient.

Cogan[2] also demonstrated tonicity of accommodation in one patient with Horner's syndrome. Our patient's long refixation time of ten seconds might result from combined sympathetic and parasympathetic abnormalities.

One might consider our patient's improvement in accommodative paresis on administration of edrophonium chloride as another facet of the supersensitivity of her ciliary muscle to 0.25% pilocarpine.

As theorized by Loewenfeld and Thompson,[9] Adie's syndrome probably results from a lesion in the ciliary ganglion. Such a lesion could conceivably damage the sympathetic fibers that traverse it and cause a Horner's syndrome. No report

has heretofore linked a Horner's syndrome with an Adie's syndrome or a pupil-sparing Adie's syndrome on the same side. Our patient's computed tomographic scan did not reveal any orbital pathology, and on hydroxyamphetamine testing, the Horner's syndrome appeared to be preganglionic.

Summary

In a 12-year-old girl with Horner's syndrome and an ipsilateral accommodative paresis, intravenous administration of edrophonium chloride improved the accommodative defect on several occasions, which suggested a possible relationship to myasthenia gravis. Additional testing of the accommodative paresis revealed some of the characteristics of Adie's syndrome and suggested a relationship to pupil-sparing Adie's syndrome.

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PERSISTENT PUPILLARY MEMBRANE ASSOCIATED WITH ANIRIDIA

NANCY HAMMING, M.D., AND JACOB WILENSKY, M.D.
Chicago, Illinois

Aniridia is a condition in which the iris appears to be absent, although gonioscopic examination usually reveals some rudimentary iris.[1,2] Although it may occur sporadically, this anomaly is often transmitted as an autosomal dominant with high penetrance and variable expressivity. The equator of the lens, the ciliary processes, and the zonules are visible as a result of the absent iris tissue. Associated conditions may include cataract, absent fovea, small optic disk, nystagmus, peripheral corneal vascularization, and angle abnormalities that may cause juvenile glaucoma. The embryologic defect in aniridia is the subject of some controversy.

CASE REPORT

A 12-day-old white male infant was first seen here in April 1976. When he was initially examined at 5 days of age, a diagnosis of bilateral aniridia was made. The infant was the product of a normal, full-term pregnancy and an uncomplicated delivery. Growth and development of the baby up to 8 months of age have been normal.

The child's 21-year-old mother had congenital bilateral aniridia and poor vision. Her best corrected visual acuity was 6/120 (20/400) in both eyes. External ocular examination revealed a pendular nystagmus. The corneas had central, superficial stromal opacities with vessel ingrowth secondary to recurrent corneal ulceration. No iris was visible on slit-lamp examination in either eye. Applanation pressures were within normal limits. Although the corneal opacities somewhat obscured the fundus, no definite abnormalities could be identified. Her parents allegedly had no ocular abnormalities; however, her maternal grandmother and a maternal aunt were reported to have had poor vision since childhood.

The 46-year-old father of the baby stated that he had been blind in both eyes following several episodes of trauma to the head. He refused to have an ophthalmic examination.

The patient was examined under anesthesia June 14 and Nov. 18, 1976. On both occasions, external examination was within normal limits. Retinoscopy revealed a +3.50 diopter spherical correction in both eyes. The corneas were clear and normal in size. Gonioscopic examination showed grade 3 angles open to ciliary body. A 1-mm iris remnant was visible for 360 degrees with well-developed arcades of vessels ramifying over the anterior surface of the lens from the iris remnant (Fig. 1). The iris was slightly scalloped, and the vessels spread from the peak of the scallops across the lens (Fig. 2). At least one vessel was patent and contained red blood cells. Intraocular pressure measured by applanation tonometry was between 8 and 11 mm Hg bilaterally. Although the lenses were clear on initial examination, a small posterior subcapsular opacity was noted in the right lens during the second examination. Fundus examination disclosed poor foveal reflexes bilaterally; the optic disks appeared normal with a 0.3 cup:disk ratio. The peripheral fundus examination was normal.

The systemic physical examination was unremarkable. Routine laboratory tests, including an intravenous pyelogram, showed no abnormalities.

DISCUSSION

Embryologically, the primitive mesodermal iris begins to form at the 17-mm stage, at which time small capillary buds arise anterior to the lens.[2] These blood vessels communicate with the hyaloid

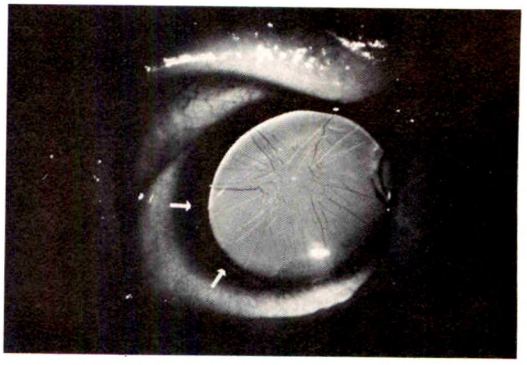


Fig. 1 (Hamming and Wilensky). The vascular arcades are on the anterior surface of the lens. The iris remnant (arrows) is peripheral to the lens equator.

From the Department of Ophthalmology, University of Illinois Abraham Lincoln School of Medicine, Chicago, Illinois. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., and a research grant from the Illinois Society for the Prevention of Blindness.

Reprint requests to Jacob Wilensky, M.D., University of Illinois Eye and Ear Infirmary, 1855 W. Taylor St., Chicago, IL 60612.

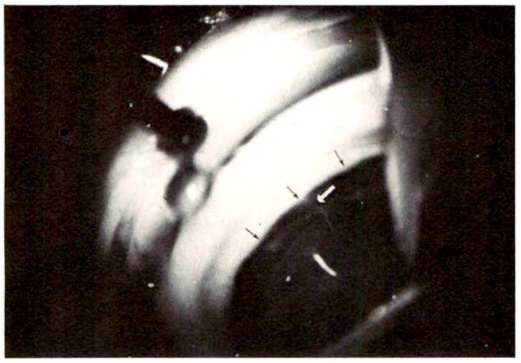


Fig. 2 (Hamming and Wilensky). Goniophotograph showing vessel (white arrow) bridging the gap from the iris remnant to the lens surface. Note scalloped character of iris margin (black arrows).

vascular system by an anastomotic connection via the lateral tunica vasculosa lentis. Beginning at the 48-mm stage, the neuroectodermal optic cup grows forward along the mesodermal scaffolding of the iris. When this forward growth occurs, the anastomotic connection between anterior and lateral tunica lentis disappears.

Two main theories have been proposed to explain the primary cause of congenital aniridia.[1] One holds that the defect is neuroectodermal, whereas the second suggests it is mesodermal. Some investigators believe aniridia is not an entity in itself, but rather the phenotypic expression of several different embryologic defects.[3]

The theory that aniridia is a result of a neuroectodermal defect implies a primary failure of development of the rim of the optic cup at the 48-mm stage. Support for this theory is the presence of other ectodermal defects that often are associated with aniridia: absence of fovea, poorly developed ciliary processes, and lens anomalies. Contrary to this theory, mesodermal iris normally forms before ectodermal iris. In most reported cases of aniridia, most mesodermal elements are absent. The lack of an inductive role by the ectoderm at the rim of the optic cup may account for the absence of these elements.[4] Alternatively, the mesoderm may form normally, but subsequently degenerate early in embyronic life because of the absence of ectodermal iris.[5]

Aberrant development of mesoderm may take several forms. Because the mesodermal elements normally form a scaffolding for the anterior growth of the optic cup, a primary failure of the mesodermal growth could arrest any subsequent ectodermal development. The lateral tunica vasculosa lentis (capsulopupillary vessels) normally connect the vessels of the embryonic hyaloid vascular system with those of the anterior tunica vasculosa lentis (primitive pupillary membrane). Failure to regress could result in partial (coloboma) or complete (aniridia) inhibition of forward growth of ectodermal iris. Coats,[6,7] Hess,[8] Mann,[5,9] and Barber[10] believe that persistence of vascular strands around the rim of the optic cup may explain atypical colobomata, multiple colobomata, polycoria, and lens opacities, as well as aniridia. In the major pedigree studies of aniridia, however, a few cases of associated persistent pupillary membrane were reported.[3,11,12]

Our patient had a well developed pupillary membrane at 2½ and 8½ months of age. The presence of a pupillary membrane has two major pathogenetic possibilities. First, persistence of the lateral tunica vasculosa lentis connecting these vessels with the primitive hyaloid system could prevent the normal forward growth of ectodermal iris. The vessels of the lateral tunica might atrophy before birth and leave no evidence of their growth-retarding influences. However, since the pupillary membrane remains completely intact, the lateral tunica probably would not atrophy completely.

A second and more probable explanation of aniridia is the primary failure of neuroectodermal growth. The presence of a normal pupillary membrane that should have provided proper scaffolding over

which the iris could grow and the presence of other ectodermal defects (cataract and macular hypoplasia) support this theory.

SUMMARY

Familial aniridia is an autosomal dominant condition in which only a small iris remnant is present. A controversy exists as to whether the pathogenetic, embryologic origin of this condition is neuroectodermal or mesodermal.

We examined a male infant with bilateral congenital aniridia associated with persistent pupillary membranes. This child had a prominent arcade of vessels extending onto the anterior lens surface for 360 degrees from small iris remnants in both eyes. The presence of a mesodermal pupillary membrane despite absence of the iris suggested a primary neuroectodermal defect as the pathogenetic factor in this case of aniridia.

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A COLLAGENASE DIGESTION METHOD FOR BIOASSAY OF ANTIBIOTICS IN OCULAR TISSUES

MICHAEL BARZA, M.D., ANNE KANE, A.B., AND JULES BAUM, M.D.

Boston, Massachusetts

The measurement of antibiotic concentrations in various fluids by agar-diffusion bioassay is well established; however, the application of this technique to tissue samples presents special problems. One approach is to homogenize the tissue mechanically in a liquid medium and to assay the drug in the supernatant fluid.[1-4] This method does not insure a uniform distribution of drug between tissue and supernatant fluid and is technically awkward. A recently described modified trephine-disk bioassay[5] seems satisfactory for routine purposes. In other instances, however, the nature, shape, or consistency of the tissue may require another approach. Therefore, we have developed a procedure of enzymatic digestion of ocular tissues with bioassay of the resultant mixture. We describe herein our results using this method to assay tissues that have been impregnated with antibiotics in vitro and in vivo. We studied representative penicillins, cephalosporins, and aminoglyosides as well as clindamycin and vancomycin. In the second group we included cefamandole, an investigational cephalosporin with an extended spectrum of activity.[6]

MATERIAL AND METHODS

Preliminary in vitro experiments showed that the following enzyme preparations were effective in digesting ocular tissues: (1) pronase, 20 mg/ml in TRIS buffer, pH 8.0, at 37° C overnight; (2) papain, 2 mg/ml in cysteine acetate buffer, pH 7.3, at 50° C for two hours; (3) collagenase (Sigma Type I), 1000 units/ml in barbital acetate buffer (Michaelis' barbital sodium acetate buffer), with 5 μM of $CaCl_2$, pH 7.4, at 37° C overnight. There was a striking loss of activity (>95%) of penicillin G at initial concentrations of 100 μg/ml in TRIS and in cysteine acetate buffer under the conditions described above. Because barbital acetate buffer did not exhibit this problem, we did further studies using collagenase in this medium. We did not investigate the tissue-digesting activity of pronase or papain in barbital acetate buffer.

To insure that the enzymatic solution itself would not affect the activity of various commonly used antibiotics, the following agents were dissolved in concentrations of 5, 10, 25, and 50 μg/ml of collagenase-buffer: penicillin G, oxacillin, carbenicillin, cephalothin, cefazolin, cefamandole, vancomycin, gentamicin, and tobramycin. Standards were prepared both in barbital acetate buffer (without collagenase) and in phosphate-buffered saline. The test solutions were assayed after overnight storage at 37° C and at 4° C using an agar-diffusion bioassay with *Bacillus subtilis* as the test organism.[7]

Having determined that the collagenase-buffer solution did not significantly affect the activity of various antibiotics in vitro, we examined the influence of preformed digests of ocular tissues on this activity. Cornea, sclera, and iris were obtained from albino (New Zealand white) and pigmented (Dutch belted) rabbits. The tissues were digested overnight at 37° C in collagenase solution in a volume equal to three times the weight

From the Departments of Medicine (Infectious Disease Service) (Dr. Barza), and Ophthalmology (Ms. Kane and Dr. Baum), New England Medical Center Hospital and Tufts University School of Medicine, Boston, Massachusetts. This study was supported in part by research grant EY01517 from the National Eye Institute.

Reprint requests to Jules Baum, M.D., 171 Harrison Ave., Boston, MA 02111.

of the tissue. The resulting mixtures contained a fine granular debris that was finely dispersed by vigorous vortex agitation. The digests were sterile on subculture and were stored at −20° C. Test solutions were prepared by adding 0.2 ml of a concentrated solution of the antibiotic in collagenase to 0.8 ml of tissue digest to yield final antibiotic concentrations of 5, 10, 25, and 50 μg/ml. The resulting suspensions contained 20% tissue digest (W/V). Standards were prepared in phosphate-buffered saline and collagenase-containing barbital acetate buffer.

The tissue-containing solutions were subjected to agar-diffursion bioassay immediately after preparation[7]; *B. subtilis* served as the test organism for all drugs except clindamycin, which was assayed by using *Sarcina lutea*. The digests and the standard solutions were then incubated at 37° C and were reassayed after 18 hours. Suspensions were thoroughly mixed by vortex just before each assay.

We used 13 healthy pigmented (Dutch belted) and 12 albino (New Zealand white) rabbits for in vivo studies. Each animal was given bilateral subconjunctival injections of radioactive carbon (^{14}C) labeled penicillin G, ^{14}C-labeled cefamandole nafate, or ^{14}C-labeled gentamicin sulfate. The drugs were administered in a volume of 0.5 ml at the 12 o'clock meridian 3 to 4 mm from the corneoscleral limbus. Each dose of penicillin G contained 50 μCi of radioactivity and 25 mg of bioactive drug; for cefamandole, the comparable values were 7.2 μCi and 6.25 mg of bioactive material, and for gentamicin, 6.28 μCi and 5 mg.

One hour after administration of the antibiotic, the eyes were marked with crystal violet to maintain geographic orientation. The animals were then killed and the eyes removed. Aqueous humor was aspirated from those animals that had received cefamandole, and both aqueous and vitreous humors from those that had received gentamicin. The cornea was divided into superior and inferior halves, whereas the iris was excised as a single piece. The sclera was cut into six leaflike segments extending back nearly to the optic nerve and including the attached choroid and retina (Fig. 1). The choroid-retina was dissected as a unit from the superior three segments and was pooled; the same was done with the tissues of the inferior segments. However, only four segments of sclera and choroid-retina were demarcated for animals given gentamicin (Fig. 2).

Each specimen of ocular tissue was minced, weighed in a sterile vial, and mixed with collagenase solution (1000 units of Sigma Type I collagenase per milliliter of barbital acetate buffer containing 5 mM of calcium chloride, pH 7.4) to yield a 10% (W/V) tissue digest. Standard solutions for the bioassay were prepared by diluting the original antibiotics in collagenase-barbital buffer. Tissue digests and standards were incubated overnight at 37° C.

Each sample was assayed by two methods: bioassay and radioassay. Bioassays were done by the agar-diffusion technique using *B. subtilis* as the test organism.[7] For the radioassay, 0.05 or 0.1 ml of each suspension was placed in 1.0 ml of Protosol. Liquifluor was added and the resulting mixture was subjected to scintillation counting.[5] Quench correction was performed by the external standards-channels ratio method. Results obtained by radioassay were expressed in terms of bioactive drug as determined by bioassay of the stock solution.

RESULTS

In our in vitro studies, there was no significant loss of activity of penicillin

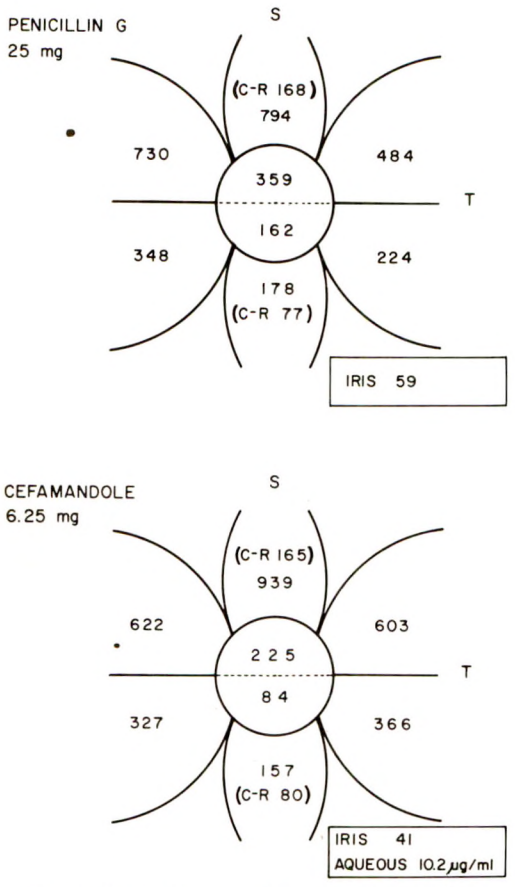


Fig. 1 (Barza, Kane, and Baum). Mean concentrations (µg/g) of antibiotic (radioactive assay) in ocular tissues of pigmented and albino rabbits one hour after subconjunctival injection of penicillin G, 25 mg (top) and cefamandole, 6.25 mg (bottom). The six peripheral values indicate sclera; C-R designates the combined specimen of choroid-retina taken as a unit from the superior or inferior scleral segments. Values in the central circle denote superior or inferior cornea. Data represent the mean of approximately 24 specimens for penicillin G and approximately 17 for cefamandole nafate. S designates superior; T designates temporal.

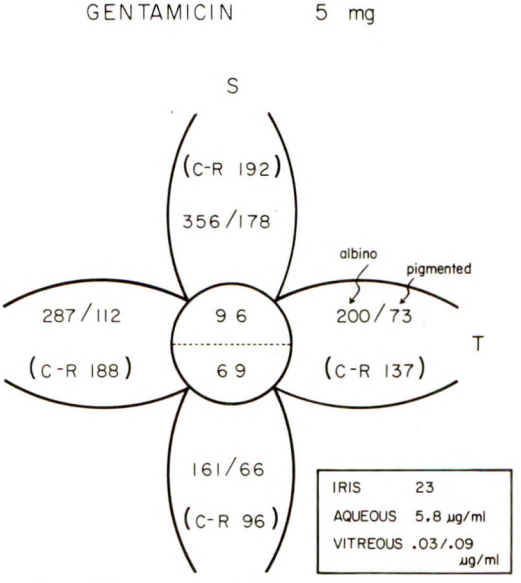


Fig. 2 (Barza, Kane, and Baum). Mean concentrations (µg/g) of gentamicin (radioactive assay) in ocular tissues one hour after subconjunctival injection of 5 mg of bioactive antibiotic. Values to the left of the slash marks indicate results for albino rabbits; those to the right are for pigmented animals. Data in parentheses refer to choroid-retina. Results in the central circle pertain to superior or inferior cornea. Values are the mean of 8 to 16 specimens of tissue. S designates superior; T designates temporal.

G, oxacillin, carbenicillin, cephalothin, cefazolin, cefamandole, vancomycin, gentamicin, or tobramycin in collagenase-barbital acetate buffer solutions as compared to standards prepared either in the buffer alone or in phosphate-buffered saline and maintained under the same conditions (37° C or 4° C for 18 hours). Moreover, standard curves prepared in barbital acetate buffer were virtually superimposable on those prepared in phosphate-buffered saline. The necessity of maintaining the antibiotic standards at the same temperature as the test solutions was emphasized by the observation that penicillin G, oxacillin, cephalothin, cefamandole, and vancomycin all demonstrated marked losses of activity (10 to 38%) at 37° C as opposed to 4° C.

The results of assays of tissue digests to which known concentrations of antibiotics were added are shown (Table 1). The only substantial interactions were those of iris with gentamicin or tobramycin; these showed slight loss of activity in digests from albino rabbits, but complete disappearance of detectable drug in sus-

TABLE 1

EFFECT OF COLLAGENASE TISSUE DIGESTS ON THE ACTIVITY OF ANTIBIOTICS

Antibiotic and Breed	Percentage Change in Antibiotic Activity after 18 Hours of Exposure to Tissue Digests (20% W/V)*		
	Cornea	Sclera	Iris
Penicillin G			
Pigmented	15 ± 4	9 ± 3	−1 ± 3
Albino	9 ± 3	18 ± 4	15 ± 3
Oxacillin			
Pigmented	2 ± 2	N.D.†	12 ± 2
Cefamandole			
Pigmented	5 ± 1	N.D.†	−2 ± 2
Cefazolin			
Pigmented	3 ± 1	6 ± 2	7 ± 3
Vancomycin			
Pigmented	−5 ± 3	−8 ± 1	−18 ± 2
Albino	0 ± 4	9 ± 6	−6 ± 6
Clindamycin			
Pigmented	9 ± 3	19 ± 6	10 ± 4
Gentamicin			
Pigmented	−4 ± 2	4 ± 4	None detectable
Albino	10 ± 3	9 ± 2	−24 ± 2
Tobramycin			
Pigmented	−2 ± 6	−11 ± 4	None detectable
Albino	1 ± 1	−3 ± 3	−20 ± 3

*Results of studies with high (25 or 50 μg/ml) and low (5 or 10 μg/ml) concentrations of antibiotic have been combined; each value is the mean and standard error of four to six samples.

†Not done.

pensions from pigmented rabbits. The effect was as striking immediately after preparation of the mixtures as after 18 hours.

We studied penicillin G in vivo in 16 to 65 specimens of cornea, sclera, choroid-retina, and iris in each strain of rabbit. The same was true of cefamandole except only eight specimens of iris were examined from each breed. The mean concentrations of penicillin G and cefamandole in the various ocular tissues as measured by radioassay are shown schematically (Fig. 1). The results for pigmented and albino rabbits were virtually identical and were combined. Although the dose of penicillin G was four times that of cefamandole, the concentrations in the cornea and the iris showed only a twofold difference and those in sclera and choroid-retina were comparable to the two agents in these noninflamed eyes. The mean aqueous level measured in eyes receiving cefamandole was 10.2 μg/ml.

For each sample, the bioassay result was expressed as a percentage of the radioactive assay value. The mean divergence of the former from the latter for both drugs in the two strains of rabbits is shown (Table 2). The differences were minor except for the iris, which showed an underreading with penicillin G of almost 50% by bioassay in both breeds. The majority of individual samples of each tissue yielded a bioassay result that was within 20% of the radioactive assay, except for penicillin G in the iris.

Gentamicin in vivo (Fig. 2) produced intraocular drug concentrations which were about one-half those of cefamandole given in a similar dosage. In contrast to the findings with penicillin G and cefamandole, pigmented and albino rabbits differed in the amount of radioactive drug detectable in the sclera (values are separated by slash marks in Figure 2). Between the strains of rabbits, no such disparities in content of radioactive drug in other ocular tissues or fluids were found.

The radioactive and bioassay results for gentamicin hardly differed in any of the albino tissues or in the cornea or sclera of pigmented rabbits (Table 2); however, there was a striking underreading by the bioassay with regard to choroid-retina and iris from pigmented animals. These findings agree with the results when gen-

TABLE 2

CORRELATION BETWEEN RADIOACTIVE ASSAY AND COLLAGENASE DIGEST BIOASSAY ^{14}C-LABELED PENICILLIN G, CEFAMANDOLE, AND GENTAMICIN

Tissue and Breed	Percentage Divergence of Bioassay from Radioactive Assay Value (Mean and Standard Error)*			Percentage of Bioassay Values within 20% of Corresponding Radioactive Assay Value		
	Penicillin G	Cefamandole	Gentamicin	Penicillin G	Cefamandole	Gentamicin
Pigmented rabbits						
Cornea	−8 ± 2	7 ± 3	17 ± 10	80	80	57
Sclera	1 ± 2	−2 ± 2	−1 ± 6	85	91	67
Choroid-retina	6 ± 3	2 ± 2	>−59	75	100	0
Iris	−46 ± 3	1 ± 4	>−79	0	89	12
Albino rabbits						
Cornea	−16 ± 3	6 ± 3	3 ± 6	66	88	88
Sclera	−1 ± 2	4 ± 1	4 ± 3	80	89	100
Choroid-retina	−8 ± 4	4 ± 3	−12 ± 5	70	100	73
Iris	−45 ± 3	1 ± 2	12 ± 6	0	100	88

*Negative values indicate less activity by bioassay than by radioactive assay.

tamicin was added to digests of ocular tissues in vitro.

DISCUSSION

We developed a method for the assay of antibiotics in homogenates of ocular tissues. Previous techniques relied primarily on physical disruption,[1-4] which is tedious and likely to produce particles of markedly varying dimensions. Generally, the supernatant fluid from such homogenates rather than the whole suspension is assayed on the assumption that the antibiotic will be freely liberated from the tissue fragments; however, the validity of this assumption has not been demonstrated. The method we outlined obviates many of these problems insofar as the enzymatic digestion produces a fine suspension in which tissue particles as well as ambient fluid are taken up by the filter-paper disk used for the assay. In case of uncertainty about the readiness with which particulate matter is absorbed by the paper disks, an agar-well, cup-plate, or cylinder modification of the agar-diffusion bioassay may be used.

Several enzymes produced excellent degradation of ocular tissues, but the accompanying buffers destroyed penicillin G. Therefore, these studies were conducted with collagenase in barbital acetate buffer, a combination which did not affect the activity of penicillins, cephalosporins, aminoglycosides, or vancomycin. We observed no difference between standard curves prepared in barbital acetate buffer and those prepared in phosphate-buffered saline; nevertheless, because of the striking effects that the diluent may have upon the results of such assays,[8,9] we strongly advise that the standards be prepared in a medium that closely corresponds to that of the specimens being assayed. Because loss of activity of several penicillins, cephalosporins, and vanomycin occurred at 37° C as compared to 4° C, it is necessary to incubate the standards at the same temperature as the samples being digested.

Having established that the collagenase-buffer solution did not affect the antibiotics of interest, we examined the influence of tissue digests. Because it was

difficult to obtain sufficient amounts of choroid or retina, they were not studied in vitro. Preformed digests of cornea, sclera, and iris were incubated with representative beta-lactam antibiotics (penicillin G, oxacillin, cefazolin, cefamandole) and aminoglycosides (gentamicin, tobramycin), as well as examples of other classes (clindamycin, vancomycin). We noted no important interaction between any of the antimicrobial agents and tissues, except both gentamicin and tobramycin exhibited a minimal (20 to 24%) decrease in activity in suspensions of iris from albino rabbits, and a complete disappearance of detectable drug in iris digests from pigmented animals. This effect, which appeared immediately after the mixtures were prepared, suggests a prompt and largely irreversible interaction between these aminoglycoside antibiotics and iris tissue in vitro.

The ability of homogenates of various organs,[10] pus,[11] feces,[12] and melanin[13] to bind or otherwise inactivate antibiotics such as gentamicin and tobramycin is well documented. Similar effects were reported with clindamycin and vancomycin,[10] penicillin G, cephalothin, and erythromycin.[14] Our inability to detect binding of clindamycin, vancomycin, or penicillin G contrasts with the experience of others,[4,10,14] and could be the result of differences in the tissues studied as well as to the possible effect of collagenase on the receptor sites for these agents.

Once we realized that exogenously added antibiotics were readily detectable in preformed ocular tissue digests (with the exception of aminoglycosides in the iris), we examined the accuracy of the assay for tissues that had been impregnated with antibiotic in vivo. Penicillin G, cefamandole, or gentamicin was injected subconjunctivally, and their concentrations were assayed in cornea, sclera, iris, and choroid-retina. An excellent correlation emerged between the collagenase digestion bioassay and the radioactive assay with two exceptions: (1) iris digests from both strains of rabbits exhibited almost 50% less bioactivity than radioactivity with penicillin G; and (2) choroid-retina and iris from pigmented animals contained strikingly less gentamicin by bioassay than by radioassay. The findings with penicillin G were surprising because no such interaction was evident with the preformed digests of iris tissue (Table 1). Although the specimens may have contained some ciliary body, which actively transports organic anions such as penicillin G, any special receptor sites probably would have been destroyed during digestion. However, we cannot rule out the possibility that stable binding to iris or ciliary body occurs when a drug is applied in vivo, but not in vitro.

The amounts of radioactive gentamicin detectable in the iris or choroid-retina did not differ between the strains of rabbits. In contrast, concentrations detectable by bioassay differed markedly between strains with much lower levels recorded in the iris and choroid-retina of pigmented than of albino animals. Because there are no known gentamicin-inactivating enzymes in animal tissues, the discrepancy can most readily by attributed to binding of antibiotic by these pigmented tissues. In support of the notion that putative binding materials involve melanin, both in vitro (preformed digests) and in vivo, the phenomenon was most pronounced in pigmented tissues (iris and choroid-retina as opposed to cornea and sclera) from pigmented animals. Moreover, melanin inactivates aminoglycoside antibiotics.[13] Although we found a slight degree of binding by albino iris digests, this was neither apparent in vivo nor was it evident in a previous study using different techniques.[5] Therefore, the interaction must be exceedingly weak.

The mechanism of the interaction between aminoglycosides and pigmented ocular tissues is unknown; however, it does not appear to be a product of digestion because almost identical results were obtained in similar experiments comparing the trephine-disk agar-diffusion bioassay with radioactive assay of gentamicin. Again, there was a marked underreading by bioassay of the amount of antibiotic in pigmented ocular tissues. These findings should not be interpreted to indicate that the bioassays (collagenase-digestion or trephine-disk) are incorrect; rather, they measure diffusible drug, whereas radioactive assays detect total drug. The former may be the most relevant value in terms of clinical efficacy. By correlating the results of diffusion bioassay with those of radioactive assay, the investigator may infer the presence of binding or degradation of antibiotics in tissues and fluids.

The collagenase digestion agar-diffusion method provides a simple and convenient means to bioassay antibiotics in ocular tissues. Although the trephine-disk technique is more convenient and equally reliable for most purposes,[5] some situations may require tissue homogenization. A disparity between the results of diffusion bioassays and other kinds of assays may suggest a variety of specific interactions. These discrepancies reflect antibiotic binding or accumulation.

SUMMARY

We assayed antibiotics in ocular tissues with a new technique involving collagenase digestion followed by agar-diffusion bioassay of the resultant suspension. The collagenase enzyme did not influence the activity of antibiotics. Similarly, incubation of a variety of antimicrobial agents with preformed digests of cornea, sclera, and iris did not interfere with the assay, except the activity of aminoglycosides (gentamicin, tobramycin) was strikingly reduced in iris digests from pigmented rabbits and was slightly diminished in those from albino animals.

We administered radioactive antibiotics subconjunctivally to rabbits and then performed bioassay and radioactive assay on the digests of the ocular tissues. The results of the two measurements were similar for penicillin G and cefamandole except there was a moderate underestimate of penicillin G in the iris. Although gentamicin was present in similar quantities in the ocular tissues of pigmented and albino rabbits (as determined by radioactive assay), it was barely detectable by bioassay in the iris and the choroid-retina from pigmented animals. These findings and other data suggest that melanin-containing tissues tightly bind aminoglycosides. The collagenase-digestion bioassay is convenient for assaying diffusible antibiotic in ocular tissues; coupled with another technique, such as radioactive assay, it can provide evidence of binding of antibiotics by tissues.

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OPHTHALMIC MINIATURE

"I'll tell you what happened," said Baley. "You were at the dome when you dropped your glasses. You must have been nervous and I've seen you when you're nervous. You take them off, you wipe them. You did that then. But your hands were shaking and you dropped them; maybe you stepped on them. Anyway, they were broken, and just then, the door opened and a figure that looked Daneel faced you.

You blasted him, scrabbled up the remains of your glasses, and ran. When they came to find you, you discovered that it was not Daneel, but Dr. Sarton, that you had killed. Without your glasses in that moment of tension, you could not tell them apart."

Isaac Asimov, *The Caves Of Steel*
Panther Books, 1958

ANIRIDIA, CATARACTS, AND WILMS' TUMOR IN MONOZYGOUS TWINS

EDWARD COTLIER, M.D., MARC ROSE, AND STEVEN A. MOEL

Chicago, Illinois

The association of Wilms' tumor and aniridia in humans demonstrates a link between the inherited and mutagenic effects of genes and their expression[1–5] and represents a joint manifestation of cancer and a congenital structural tissue defect. According to Knudson,[6] the expression of the Wilms' tumor gene may result from two mutational events. In the dominantly inherited form, one mutation is inherited via the germinal cells, and the other, in somatic cells. In the nonhereditary form, both mutations occur in somatic cells.[6] Knudson[7] has developed a similar theory to explain inherited and nonherited forms of retinoblastoma. The genetic basis for the development of Wilms' tumor is firmly supported by its familial nature,[8–14] and by its occurrence in monozygous twins.[15–18] The explanation for the genetic mutation in the Wilms' tumor-aniridia syndrome appears more complex. In one patient with the syndrome, a chromosmal translocation was found,[19] but such an occurence has not been reported in families. We describe a heretofore unreported genetic curiosity in identical twins, both of whom have bilateral aniridia and cataracts, but only one of whom has Wilms' tumor.

CASE REPORT

Twin girls were born after a full-term pregnancy to a 32-year-old mother and a 39-year-old father, both of whom were phenotypically normal. Fetal movements were felt at 4½ months of pregnancy. The mother gained 42 pounds during gestation. She had no fever, viral infection, or exposure to teratogenic chemicals during pregnancy, but she did have several episodes of vaginal bleeding. Calcium and iron medications were prescribed during the last months of the pregnancy. Labor was difficult and lasted four hours, and delivery occurred under general anesthesia.

The twins had three brothers: two, aged 15 and 14 years, respectively, without phenotypic abnormalities; and one who had had multiple congenital malformations including cleft palate, syndactyly, and psychomotor retardation, and who had died of pneumonia at the age of 4 years. Neither side of the family had a history of consanguineous marriage, mental retardation, or neurologic disease. A maternal uncle had had congenital cataracts in both eyes, and each side of the family had a history of diabetes mellitus. The family pedigree appears in Figure 1.

Case 1—At birth, the younger twin (Fig. 2, left) weighed 2,353 g. Shortly thereafter, aniridia and cataracts were detected in her. When she was 5 months old, an examination under anesthesia revealed bilateral increased intraocular pressure, which was treated with pilocarpine 4% drops to both eyes three times a day. When the child was 3 years old, the mother noted a lump on the left side of the child's abdomen. An intravenous pyelogram revealed a large mass in the left kidney and delayed excretion of dye with distorted calyces. An exploratory laparotomy revealed on the left side a Wilm's tumor, which was removed. Thirteen months later, a contralateral Wilms' tumor was found, and a right heminephrectomy was performed. After each resection, radiotherapy was given, supplemented with actinomycin D therapy (15 mg/kg of body weight) to the retroperitoneal area. The second course of radia-

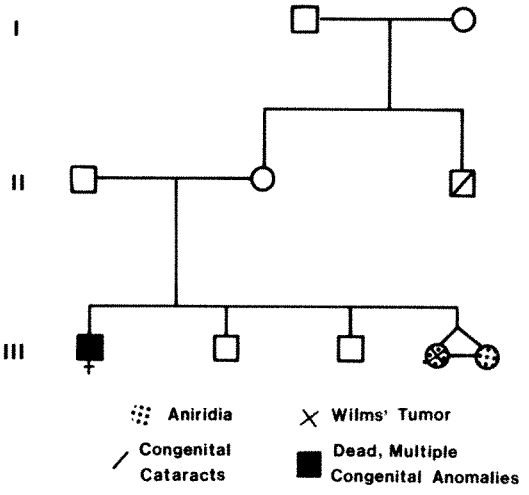


Fig. 1 (Cotlier, Rose, and Moel). Pedigree of family with aniridia and Wilms' tumor in identical twins.

From the University of Illinois Eye and Ear Infirmary, Chicago, Illinois.

Reprint requests to Edward Cotlier, M.D., Department of Ophthalmology and Visual Science, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06510.



Fig. 2 (Cotlier, Rose, and Moel). Left, Case 1. The younger twin with aniridia and Wilms' tumor. Right, Case 2. The older twin with aniridia but clinically free of Wilms' tumor.

tion was interrupted when the child developed right lower lobe pneumonitis, urinary tract infection, and persistent fever, all of which responded well to antibiotic therapy. Radiotherapy was then resumed and the course completed.

At age 6 months, the child could turn in her bed, and by 1 year, she was able to crawl, albeit awkwardly. At 15 months, when she showed no initiative in pulling herself up to walk, a diagnosis of developmental retardation was made. At age 2 years, she was able to sit unsupported and could eat table food with her hands. However, she would not play, socialize, or react at peer level. By age 3, she was able to pull herself up, stand, and take one or two steps with support. She did not speak, but made some sounds and apparently understood a few verbal commands. She often ground her teeth. The parents noted that the child's eyes moved about in a random, searching way with rotary, jerking movements. At age 7 years, severe psychomotor retardation was diagnosed.

Complete blood cell count, urinalysis, urinary mucopolysaccharide test, amino acids in urine, and Giemsa-banded karyotype (46 XX) were normal. Electroencephalograms revealed an abnormal delta rhythm with diffuse abnormal spikes suggesting cortical and subcortical structural brain damage.

Zygosity was determined by blood-group analysis (ABO, P, Rh, Kelly, Lewis, MNS, Lutheran, Duff) and three serum factors (haptoglobin, transferrin, Gm), and the twins were found to be monozygotic.

Several eye examinations under anesthesia when the child was between 4 and 7 years of age revealed bilateral aniridia, bilateral anterior and posterior polar cataracts, bilateral myopia of −6.00, alternating exotropia of 30 prism diopters, searching nystagmus, and glaucoma (Fig. 3). Electroretinograms were normal bilaterally, and gonioscopy revealed small rudimentary iris nubs in both anterior chamber angles. An examination in April 1973 revealed intraocular pressure of 29 and 51 mm Hg in the right and left eyes, respectively, with C-values of 0.10 on the right and 0.01 on the left. The cup:disk ratio was 0.5 on the right eye, and 0.7 on the left. Administration of pilocarpine 4% drops four times a day and epinephrine 2% drops twice a day decreased the intraocular pressure to 16 mm Hg in the right eye and 22 mm Hg in the left eye.

Case 2—In the older twin (Fig. 2, right), a diagnosis of congenital aniridia, cortical cataracts, and glaucoma was made shortly after birth. At age 3 years, the child had marked psychomotor retardation with wandering eye movements and body rocking. The anteroposterior diameter of the head was shortened. The child was hyperactive and able to walk stiffly for two to three steps. She had uniformly depressed deep tendon reflexes and no superficial abdominal reflexes.

Laboratory tests including complete blood cell count and urinalysis were negative. Giemsa-banding karyotype was normal (46 XX). No evidence of Wilms' tumor was found, although depression and rotation of the left kidney was noted on the intravenous pyelogram. Repeated intravenous pyelograms during a four-year period failed to reveal any tumoral kidney growth.

Several eye examinations when the child was between 3 and 7 years of age revealed aniridia, bilateral polar cataracts, and 20 degrees exotropia in the primary gaze (Fig. 2, right). Examination under anesthesia in 1973 revealed intraocular pressure of 30 mm Hg in the right eye and 50 mm Hg in the left. Tonography gave a C-value of 0.07 for the right eye and 0.03 for the left eye. Retinoscopy revealed −5.00 diopter of bilateral myopia. The electroretinogram was within normal limits. The retina showed slight bilateral peripheral pigment mottling. Gonioscopy

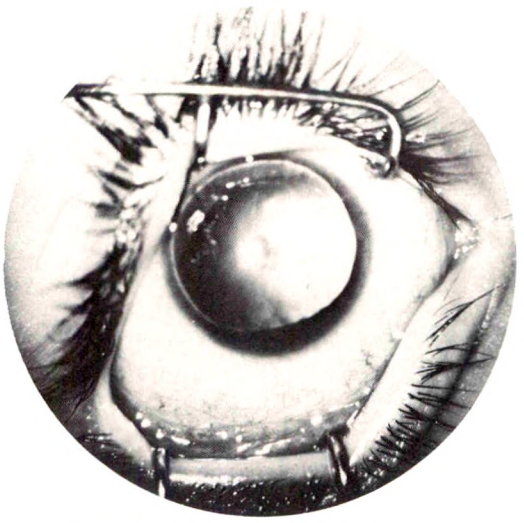


Fig. 3 (Cotlier, Rose, and Moel). Case 1. Aniridia and cortical cataracts.

revealed small rudimentary iris nubs bilaterally. The patient received pilocarpine 4% drops, four times a day and epinephrine 1% drops twice a day, with subsequent reduction of intraocular pressure to 18 mm Hg in the right eye and 22 mm Hg in the left eye.

Discussion

Wilms' tumor (nephroblastoma) is the second most common neoplasm among children. Thirty-eight percent of the cases are inherited,[6] and the remaining 62% occur at random. The inherited form occurs earlier and is much more frequently bilateral.[6] The median age at diagnosis for the noninherited Wilms' tumor is 3 to 4 years, whereas the hereditary form manifests itself at approximately 2 years of age.[6] Bilateral tumors are found in 5 to 10% of the total cases, but in 21% of the hereditary form.[6] Knudson[6] has therefore suggested a single-event prezygotic, zygotic, or immediately postzygotic mutation for the hereditary form of Wilms' tumor and a double mutation (zygotic and somatic cells) for the nonhereditary forms of the tumor. Knudson[7] previously proposed a similar concept regarding the inherited and noninherited forms of retinoblastoma. Maslow[8] was the first to report Wilms' tumor in three of four siblings. Other instances of Wilms' tumor in siblings were documented by Mackay,[9] Chapian,[10] and Collins.[11] In 1955, Fitzgerald reported Wilms' tumor in a father and in two of his three daughters,[12] and, subsequently, Brown, Puranik, Altman, and Hardin[13] found a Wilms' tumor in a 6-month-old child of the surviving daughter. Other cases of Wilms' tumor reported in families and in successive generations have been tabulated by Juberg, Martin, and Hundley.[14] Six instances of this neoplasm in twins have been reported,[1,14-18] but except for one case of identical twins, the status of zygosity in the others remains uncertain. Although the occurrence of this tumor in siblings and in twins represents overwhelming evidence for genetic mutations, the case of Juberg, Martin, and Hundley[14] in which the tumor was clinically present in only one of identical twins provides support for an environmental mutation.

The association of aniridia and Wilms' tumor was first uncovered by the review of 440 cases of the tumor by Miller, Fraumeni, and Manning.[1] They found an incidence of six aniridics among their patients with Wilms' tumor, or 1:73, which is markedly greater than the 1:50,000 incidence of aniridia among the general population.[20] Patients with Wilms' tumor alone, and with Wilms' tumor and aniridia have a higher incidence of mental retardation, hypospadias and undescended testes, and hemihypertrophy than the population of the same general age.[1,4,21] Thus, in 1964, Miller, Fraumeni, and Manning[1] questioned whether the aniridia and Wilms' tumor syndrome is genetically determined, whether the tumor results from a concurrent mutation of a different gene, or whether the aniridia gene enhances the expression of the Wilms' tumor gene. Reviewing previous studies in 1975, Piling[5] revealed 35 cases of Wilms' tumor with aniridia, but only one of them in families and none in twins. Fraumeni and Glass[2] found Wilms' tumor with associated congenital aniridia in seven of 28 children under age 4 years. Of these cases, the Wilms' tumor was present in one child on admission to the hospital, and it developed later in the six other children. When combined with the series of Miller, Fraumeni, and Manning,[1] a total of 35 infants, the Wilms' tumor developed in one third of the infants with congenital sporadic aniridia.[5] Only one case of Wilms' tumor in a child with familial aniridia has ever been reported. Expression of a dominant gene in two siblings, but with unaffected parents, occurs in gonadal mosaicism. In gonadal mosaicism, the frequency of gene expression depends on the degree of gonadal involvement. However, the twins in our study were identical, and a "pure" gonad-

al mutation would not apply to the expression of the Wilms' tumor gene. Juberg, Martin, and Hundley[14] found Wilms' tumor in one of the monozygous twins and in one other sibling. Aniridia was absent in all of these cases. Juberg, Martin, and Hundley[14] believed this pattern of gene expression supported the environmental theory of Wilms' tumor.

In our patients, we must consider the likelihood of a combined gonadal-somatic cell mutation in the younger twin and a gonadal mutation in the older twin. A gonadal somatic mutation probably occurred in a Wilms' tumor allele and a pure gonadal mosaicism affected the aniridia allele. A two-allele gonadal and a somatic mutation could explain the manifestation of Wilms' tumor in only one twin.

A more remote possibility would involve a single-locus, three-allele mutation, which for the manifestation of Wilms' tumor requires an additional somatic mutation. Lada, Atkins, and Littlefield[19] found a chromosomal translocation t (8 pt; 11q−) in a patient with both aniridia and Wilms' tumor. Computer analysis of the chromosomes was required because they appeared balanced by standard techniques including banding. Our patients' karyotypes were normal by Giemsa banding, but may have appeared abnormal by computer analysis of the chromosomes.

Summary

We studied the first instance of aniridia-Wilms' tumor syndrome in twins who were mentally retarded. Both of them had congenital aniridia, cataracts, and glaucoma; only one subsequently developed a Wilms' tumor. A two-allele, two-step mutation is the most likely explanation of this genetically abnormal syndrome in twins. The aniridia-Wilms' tumor syndrome in twins further documents the relationship of teratogenic malformations and neoplasias.

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DERMATOLOGIC REACTION IN STEVENS-JOHNSON SYNDROME AFTER OPHTHALMIC ANESTHESIA WITH PROPARACAINE HYDROCHLORIDE

BRIAN WARD, M.D., JAMES P. MCCULLEY, M.D., AND ROBERT J. SEGAL, M.D.
Stanford, California

Many drugs and toxic and infectious agents have been implicated in the production of the form of generalized erythema multiforme with mucous membrane involvement known as the Stevens-Johnson syndrome. This acute inflammatory reaction, involving many parts of the body, occurs characteristically a few days to weeks following exposure to the sensitizing agent. The ophthalmologic symptoms are severe conjunctivitis, commonly with some degree of eyelid margin involvement, and occasionally, a secondary bacterial blepharoconjunctivitis. The acute stage of the condition may rarely involve the production of conjunctival scarring and adhesions. During the chronic phase, severe conjunctival scar formation may occur with the development of symblepharon, ankyloblepharon, obliteration of the fornices, cicatricial entropion, conjunctival and corneal keratinization, trichiasis, and markedly dry eyes caused by loss of any or all of the components of the precorneal tear film.

Two recent reports[1,2] have associated the topical ophthalmic application of sodium sulfacetamide solution with the subsequent development of Stevens-Johnson syndrome. We describe herein a dermatologic reaction to a commonly used topical ophthalmic anesthetic in a patient in the acute phase of Stevens-Johnson syndrome.

From the Division of Ophthalmology (Drs. McCulley and Ward) and the Department of Dermatology (Dr. Segal), Stanford University, Stanford, California. This study was supported in part by National Institutes of Health Training Grant EY00051-09.

Reprint requests to James P. McCulley, M.D., Division of Ophthalmology, Stanford University Medical Center, Stanford, CA 94305.

CASE REPORT

A 53-year-old woman was in good general health the first week of January 1977. On January 10, oral penicillin tablets were prescribed for an upper respiratory tract infection and quinidine sulfate for irregularity of pulse. Two weeks later the patient was given phenylbutazone tablets for shoulder pain. One month later she received furosemide and reserpine. Within five days of beginning to take the latter two drugs, the patient complained of malaise and a pruritic skin eruption. Diphenhydramine hydrochloride was then prescribed. On February 12, the patient had worsening of the rash, red eyes, blisters on the mouth and lips, and fever (38.3 to 40° C). She was consequently admitted to a local hospital. When she failed to respond satisfactorily to procaine penicillin G and 100 mg of hydrocortisone daily, she was transferred to the Stanford University Medical Center Dermatology service.

When the patient was admitted to the hospital Feb. 23, 1977, her case was diagnosed as Stevens-Johnson syndrome on the basis of characteristic skin lesions and generalized mucous membrane involvement including particularly the mouth, lips, and conjunctivae. The ophthalmologic service saw the patient shortly after admission. At that time the patient had bulbar injection, marked symblepharon, and ankyloblepharon formation (Fig. 1). Conjunctival necrosis had resulted in large sheets of conjunctival tissue, which partially detached from the underlying tissues and remained attached in other areas. The free flaps of necrotic tissue had reattached



Fig. 1 (Ward, McCulley, and Segal). The eye and surrounding areas of skin on the first hospital day after extensive early symblepharon and ankyloblepharon were broken.

aberrantly and resulted in the formation of structures similar to those found in symblepharon and ankyloblepharon. The eyelid margins were ulcerated. The cornea revealed a diffuse superficial punctate keratopathy, visible with white light as well as through a cobalt blue filter after the instillation of fluorescein. The vision was generally unaffected except for variable blurring associated with debris in the precorneal tear film.

Major conjunctival adhesions were gently broken with a sterile glass rod to reform the fornices, which caused the patient some local bleeding and discomfort. We began local antibiotic applications with polymyxin B-bacitracin ophthalmic ointment every four hours. Systemic treatment consisted of intravenous hydration, potassium supplementation, and 25 mg of methylprednisolone sodium succinate by vein every six hours. The next day, the patient's general condition had improved; however, her eyes had further conjunctival adhesions. Therefore, one drop of proparacaine hydrochloride 0.5% was instilled in each eye before lysing the adhesions with a glass rod. About 30 minutes after the instillation of the topical anesthetic, and before the patient had received any further topical or systemic medication, new tense bullae with local pruritis appeared on the palms and soles and extended onto the fingers and toes (Fig. 2). These areas had not been affected previously. Additionally, the patient complained of more oral discomfort and truncal pruritis, although no change of the areas was evident on physical examination. During treatment with saline gargles, topical cleansing, emollient, and continued parenteral adrenocorticosteroids, the patient's skin condition improved progressively.



Fig. 2 (Ward, McCulley, and Segal). Bullous vesicular lesions of the palms occurring during the course of treatment.

On the second day in the hospital the patient began receiving topical ophthalmic corticosteroid therapy consisting of 0.5% dexamethasone ophthalmic ointment applied to both eyes every two hours while the patient was awake. This was tapered to four times daily over the next ten days. The systemic corticosteroid regimen was changed to 100 mg of prednisone by mouth daily on the fourth day in the hospital and was tapered to 10 mg daily by discharge on the 15th day. The lesions on the hands and feet healed in the same manner as did those on the rest of the body. By the time of discharge, the patient's eyes were less inflammed, no further symblepharon formation was noted, and the superior and inferior fornices remained full. The eyes, however, were dry, and the patient was discharged and given an artificial tear preparation to take hourly while awake, polymyxin B-bactracin ophthalmic ointment four times daily, and prednisolone 1% ophthalmic solution every four hours. To date, the patient's vision remains good despite the formation of several localized areas of symblepharon and the continued presence of a superficial punctate keratopathy.

Discussion

The prognosis for eyes involved in the Stevens-Johnson syndrome had been improved by the introduction of systemic and topical corticosteroid therapy, antibiotics, and tear replacement fluids. However, the ocular prognosis remains guarded after Stevens-Johnson syndrome, in contrast to the generally good prognosis for complete resolution of the dermatologic lesions that accompany mucous membrane involvement. The risks of recurrent corneal ulceration caused by exposure, drying, eyelid deformities, trichiasis, and poor tear film constitution are significant and may lead to corneal scarring or perforation[3] and loss of vision. The two interrelated factors that most affect the course of the condition are the scarring of the conjunctiva and the decreased tear production. All three major components of the tear film are decreased when scarring involves the ductules of the lacrimal gland, the accessory lacrimal glands, the goblet cells, and the marginal orifices of the meibomian glands.

Ocular involvement in both the acute and chronic phases requires the attention of an ophthalmologist. If our patient had not been treated, marked scars would have formed and the fornices may have disappeared permanently. The resultant distortion of anatomy would have contributed to the tear deficiency as well.

Whereas the topical ophthalmic anesthetic used in our patient was not a factor in her initial disease, clinical observations suggest its possible role in a hypersensitivity reaction resulting in an exacerbation of the Stevens-Johnson syndrome. The time course was markedly different from that normally noted between exposure to a sensitizing agent and the appearance of the classical Stevens-Johnson reaction. However, the time lapse is consistent with an immediate hypersensitivity reaction. When applied to the mucous membrane, a closely related anesthetic, tetracaine, reaches peak blood levels in about five minutes.[4] Proparacaine is a local anesthetic with an internal ester linkage similar to procaine, chloroprocaine, cyclomethycaine, hexylcaine, tetracaine, piperocaine, and naturally occurring cocaine. These local anesthetic agents are more often associated with hypersensitivity than anesthetics of the amide type such as lidocaine, mepivacaine, prilocaine, and bupivacaine.[5] Procaine penicillin G contains the anesthetic agent in significant quantities. Our patient may have failed to respond to treatment earlier because of a complicating reaction to the agent during the original hospitalization.

Two previous reports[1,2] implicate ophthalmic sulfonamide in Stevens-Johnson syndrome in generalized systemic reactions within a short time of the drug's topical application for the treatment of nonspecific conjunctivitis. In both cases, before the use of topical ophthalmic medication, the patients had been taking oral medications well known for their sensitizing properties. These topical drugs or other routine diagnostic agents might have been given during the early stages of the ocular involvement in Stevens-Johnson syndrome, before general manifestations developed. On the other hand, they might have produced immediate hypersensitivity responses directly or by cross-reaction, as we suspect happened in our patient. Therefore, in the treatment of the ocular involvement of the Stevens-Johnson syndrome, one might exacerbate the disease by using a topical drug that cross-reacts with the inciting agent.

An alternative to the ester type of local anesthetic should be considered in our patient when further anesthetic agents are indicated. Because of the remarkable sensitivity of our patient to extremely small amounts of proparacaine, we believed that scratch testing to document the nature of the allergy would be unwise.

Our patient also may have reacted to one of the additives in the commercially prepared ophthalmic drops, which produce sensitization with chronic use in some patients.[6]

SUMMARY

A 53-year-old woman, treated in the acute phase of Stevens-Johnson syndrome, received one drop of proparacaine hydrocholoride 0.5% in each eye for topical anesthesia. One hour later she developed new bullae of the hands and feet.

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NOTES, CASES AND INSTRUMENTS

RAPID ACCESS FLUORESCEIN ANGIOGRAPHY

LAWRENCE M. MERIN, B.A.
Detroit, Michigan

Image quality and processing speed are essential in fluorescein angiography. Kodak Tri-X and Plus-X films provide excellent image quality, but require from 35 to 45 minutes for conventional processing.[1] Using high temperature solutions saves processing time, but regular film emulsions soften when heated. The combination of an instrumentation film with automatic processing techniques provides high quality angiograms for analysis within 90 seconds.

MATERIAL AND METHODS

I use Kodak Linagraph Shellburst Film 2474 originally designed for missile tracking and photographing low-contrast objects in the sky. This film is a panchromatic material with an exposure index of 250. The emulsion is coated on a polyester (Estar) 4-ml thick base that is stable and tear-resistant. The film is specially hardened to withstand processing in the 32.2° C range. Using the primary developer Kodak D-19, 125 lines per millimeter are resolved for high contrast subjects. The film is available in 35 mm × 200-ft rolls that may be reloaded into Snap-Cap reusable film cartridges. I use 42 exposures in each cassette to provide enough film for leader, trailer, and 36 frames of angiography.

Rapid processing of this film is provided by a Kodak RP X-omat M-6 X-ray processing machine commonly used in radiology departments. These devices advance the film automatically through a series of heated processing solutions and then through a forced air dryer.

I use Picker 3790 developing chemistry in the X-omat at 35.6° C; other solutions should yield similar results. A completely processed dry negative is ready for viewing 90 seconds after the processing begins.

The film leader is taped to a blank X-ray film that is inserted into the loading aperture of the X-omat; the film is then pulled into the machine automatically. The film is sensitive to X-ray safelights and replenisher system indicator lights; the loading room must be in complete darkness.

RESULTS

Rapid access angiography provides more contrast than conventional films. The film base shows little fogging even after rapid development in heated solutions, which increases the contrast between fluorescein-infused structures and the film background. Initially, I used a Spectrotech E4 exciter and a B5 barrier filter (Fig. 1). Similar excellent contrast can be obtained with Spectrotech E40/B50 filters (Fig. 2). Wide-band gelatin filters increase the background density and reduce the contrast (Fig. 3). There is apparently no more graininess than with Plus-X film after forced development.

Rapid access fluorescein angiography permits revision of angiography procedures so that therapy may be started immediately after viewing the rapid access films. When photocoagulation is planned, the rapid access film provides immediate indication of the patient's status. When retinopathy is suspected in multiple fields of the posterior pole, a 20-exposure

From the Department of Ophthalmology, Sinai Hospital of Detroit, Detroit, Michigan.
Reprint requests to Lawrence M. Merin, Department of Ophthalmology, Sinai Hospital of Detroit, 6767 W. Outer Dr., Detroit, MI 48235.

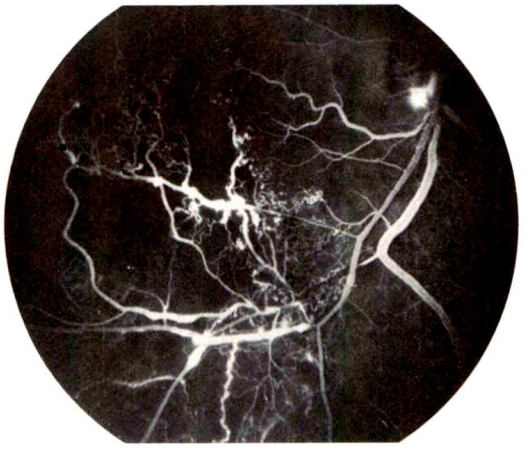


Fig. 1 (Merin). Old venous occlusion in a 69-year-old woman with moderate lens changes (Zeiss FF III, E4/B5 Spectrotech filters, flash 4). Good resolution of shunt vessels and capillaries can be achieved with these filters and the rapid access technique.

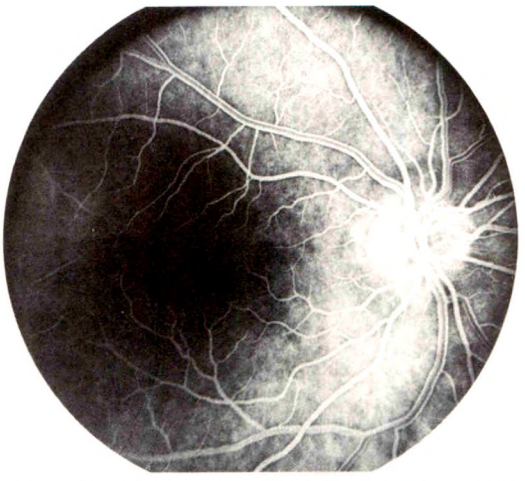


Fig. 3 (Merin). Normal angiogram of a 32-year-old man. The increased background density mainly results from the wide-band effects of Kodak Wratten 47 exciter and 15 barrier filtration.

roll may be exposed during the early phases of the dye transit and then examined to indicate in which fields late phase photography should be done.

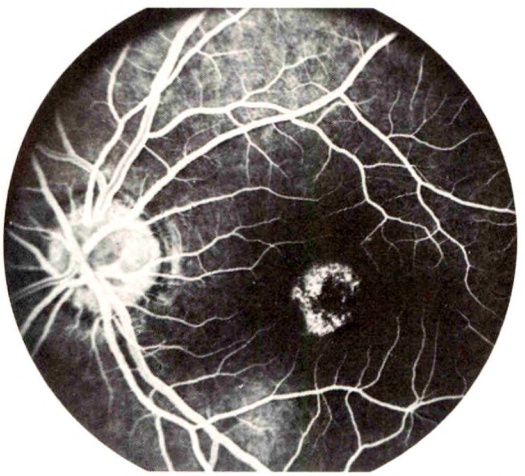


Fig. 2 (Merin). Drug-related retinopathy in a 40-year-old man. This maximum contrast is enhanced with E40/B50 Spectrotech filters and RP X-omat processed 2474 film.

The use of smaller processing machines with 2474 film could make fluorescein angiography feasible in the private office without a conventional photographic darkroom. A modified camera back would automatically advance the exposed strip of film into the processing unit, which could be an integral part of the fundus camera base.

Summary

The time interval usually required for processing fluorescein angiography films has been dramatically shortened to 90 seconds by using Kodak Linagraph Shellburst Film 2474 processed in the automatic Kodak RP X-omat processing machine, with attendant increases in image clarity and contrast.

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NONFATAL METHAZOLAMIDE-INDUCED APLASTIC ANEMIA

JOHN L. GANGITANO, M.D.,
STEPHEN H. FOSTER, M.D.,
AND RICHARD M. CONTRO, M.D.
Sacramento, California

Aplastic anemia is an uncommon, devastating, possible complication of treatment with carbonic anhydrase inhibitors. Of six reported cases of aplastic anemia caused by acetazolamide, five were fatal.[1-4] Methazolamide has been reported to the National Registry of Drug-Induced Ocular Side Effects as a possible cause of three cases of agranulocytosis and one case of leukopenia (telephone conversation with F. T. Fraunfelder, March 9, 1978). There has been one reported case of fatal aplastic anemia supposedly caused by methazolamide.[4]

We report herein a nonfatal case of aplastic anemia presumably secondary to treatment with methazolamide.

CASE REPORT

We saw an 83-year-old white man on a routine follow-up visit in the glaucoma clinic at the Sacramento Medical Center. The patient had been taking 50 mg of methazolamide three times a day for three months. Just before he began receiving methazolamide, for one month the patient had been taking acetazolamide, which was discontinued because he complained of nausea and dizziness. During the patient's visit to the clinic, he complained of epistaxis and easy bruisability. After we consulted an internist, the patient was admitted to the Hematology Service at Sacramento Medical Center. Laboratory studies on admission revealed a platelet count of 7,000 mm; a hemoglobin of 10 g/100 ml; a hematocrit of 28%; normal red blood cells on peripheral smear; a white blood cell count of 1,900 mm, with 53% granulocytes; a reticulocyte count of 0%; and a bone marrow aspirate showed 96% mononuclear cells, absent erythroid precursors, and absent megakaryocytes. A blood count done 11 months before admission had been normal.

The patient had been taking digoxin for mild congestive heart failure for five years; hydrochlorothiazide for mild hypertension for seven months; and two short courses of chlorpheniramine for nasal congestion ten and five months before admission.

A diagnosis of aplastic anemia was made. All medications were discontinued. The patient received platelet and red blood cell transfusions and was treated with oxymetholone. The patient is currently receiving packed red blood cell transfusions every three weeks. Approximately four months after initiation of treatment, when the patient was reported as feeling well, he had a white blood cell count of 4,200, with 58% granulocytes; a platelet count of 30,000; a hemoglobin of 7.0 g/100 ml; and a hematocrit of 21.5%.

DISCUSSION

Although the patient was taking several medications and an idiosyncratic reaction may have occurred, methazolamide was thought to be the cause of aplastic anemia. Acetazolamide, a related compound, may have been contributory to the disease. The only reported survivor of presumed carbonic anhydrase inhibitor marrow suppression had taken acetazolamide for just one month and had granulocytopenia only.[5] The majority of the other cases of presumed carbonic anhydrase inhibitor-induced aplastic anemia had been taking the medication for approximately three months, as in this case.

Digoxin has not been associated with aplastic anemia.[6] Thiazides have been associated with thrombocytopenia and granulocytopenia, but not with complete aplasia.[7] Chlorpheniramine is listed as a possible cause of aplasia.[8,9] In a case of pancytopenia with normal bone marrow, thrombocytopenia developed on readministration of chlorpheniramine, but the patient also had a viral illness and was receiving penicillin, both of which may have influenced his hematologic status.[10] Because of a lack of sufficient documentation of its role in aplastic anemia, chlorpheniramine cannot be considered to be a proven cause of aplasia.[11]

From the Departments of Ophthalmology (Drs. Gangitano and Contro) and Internal Medicine (Dr. Foster), University of California, Davis, Sacramento Medical Center, Sacramento, California.

Reprint requests to John L. Gangitano, M.D., 4932 Kipling Dr., Carmichael, CA 95608.

Sulfonamide-related drugs, including carbonic anhydrase inhibitors, are among the most common causes of aplastic anemia.[8] In one study, they were found to be the second most common cause of drug-induced aplastic anemia.[12] Because of the poor prognosis for carbonic anhydrase inhibitor-induced aplastic anemia, we recommend a complete blood cell count and platelet estimate for patients three to four weeks after initiation of carbonic anhydrase inhibitor therapy.

SUMMARY

An 83-year-old man developed nonfatal aplastic anemia after taking methazolamide for three months. We made a diagnosis of methazolamide-induced aplastic anemia, discontinued all medication, gave the patient platelet and red blood cell transfusions, and treated him with oxymetholone. Approximately four months after initiation of treatment, the patient felt well, and he is currently receiving packed red blood cell transfusions every three weeks.

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PRICES, PATIENTS, AND DRUG SUBSTITUTION

In view of the rising costs of prescription medicines and other health care services, many politicians, federal health planners, and consumer groups have sought programs or regulations to stabilize drug prices. These groups have tried to convince state legislators to repeal or amend antisubstitution laws, which provide that when a physician writes a prescription for a brand-name drug, the pharmacist is required to fill the prescription with the specified company's product.

These laws originated in the 1950s following the development of many new prescription drugs that resulted in the phenomenal growth of the pharmaceutical industry. During this immediate post-war period, there was widespread counterfeiting and mislabeling of prescription drugs, outright forgery of products and packaging, and uncontrolled substitution of medicines regardless of therapeutic equivalence.

In 1952 California became the first state to pass antisubstitution legislation, and eventually, all the states followed suit. In the last few years, over half the states have repealed or amended these laws to permit at least some form of substitution. Other states have similar laws under consideration. The aim of these antisubstitution law repeal movements is to allow the pharmacist, with the consumer's consent, to substitute a less expensive generic equivalent drug when the physician has prescribed a more expensive brand-name product.

Price is not the sole consideration in prescribing medication. Less expensive substitutes may not work the same way in the body as more expensive brand-name products, even though they have identical chemical structures.

Studies in biopharmaceutics, an increasingly important branch of therapeu-

tics, try to determine the ability of a drug to reach the involved body cells in effective concentration.

The preparation of a drug for use may influence its distribution in the body, the eye, and the particular involved cells. Therefore, considerable attention must be paid to bioavailability and therapeutic equivalence.

Groups opposing substitution argue that existing standards are not sufficient to guarantee that only quality products reach the consumer.

The effects of antisubstitution law repeal are now being evaluated in several states. Florida does not merely allow, but requires substitution unless the physician writes "medically necessary" on the prescription. The pharmacist is required by law to inform the patient when he substitutes and to tell the patient the exact amount of money saved. The patient has the right to refuse the substitute. Substitution appears to be making large inroads in Florida, a state that also has a negative and a positive formulary.

The negative formulary lists those generic substitutes that are not biologic or therapeutic equivalents, and the positive one lists acceptable substitutes. Saskatchewan, Canada, has had a freedom of substitution law since 1971, and in one year, the reduction of average prescription prices was barely 3%.

A substitution law that went into effect in Michigan in April 1975 caused initial dissatisfaction and confusion among physicians and pharmacists. The doctors did not use the dispense as written provision, and the pharmacists hesitated to substitute without permission of the prescribing physician. Also the pharmacist apparently needed an incentive to substitute because the profit margin on cheaper drugs is generally lower.

Liability is another potential problem. The state of California, in amending the antisubstitution law of May 1, 1976, stated that the prescribing physician would not be liable for the substitution judgment of the pharmacist. In states where repeal of the antisubstitution law has occurred but substitution is not mandatory (most states), the pharmacist, aware of potential liability resulting from dispensing inefficacious cheaper generic equivalents, may play it safe and not substitute. However, a statutory exemption that would absolve the pharmacist from liability would not be in the best interest of the consumer who then might not be protected from inferior generic drugs.

Elsewhere in this issue are the results of a recent study of the retail cost of antiglaucoma drugs in two cities. Drugs cost more in New York than in St. Louis.

New York has a substitution law and Missouri does not. However, generic substitution was not significantly greater in New York. Actually, little generic substitution occurred in either city. The price range in each city varied greatly, and the price of a drug was influenced by the style and appearance of the buyer, the neighborhood, type of store, and type of services offered by the pharmacy. These factors far outweighed the generic question in determining the cost of a prescription drug. Since 1970, 31 states (including the District of Columbia) have enacted legislation permitting some form of prescription drug substitution to reduce the cost of drugs to the consumer.

These changes do not seem to have saved the consumer a significant quantity of money. They have increased the work load slightly for the physician who must now decide whether to protect his prescription by writing additional orders, for example, "do not substitute" (New Jersey, New York, Pennsylvania), "medically necessary" (Florida), or "substitution prohibited" (Kentucky); for the pharmacist who now may have to comply with

fellow pharmacists and keep records of all substitutions, and for lawyers, both those in the Congress and Senate from states where such laws are made and amended and those who deal with liability.

IRVING H. LEOPOLD

WELCOME: THE AMERICAN SOCIETY OF OPHTHALMIC REGISTERED NURSES

The American Society of Ophthalmic Registered Nurses first met in Las Vegas October 7, 1976, in order to establish an organization dedicated to excellence in ophthalmic nursing. The founders believed that such a society would further continuing education through study, discussion, and exchange of information in the field.

In 1977, the theme of the meeting was "Insight Into Eyesight." Ophthalmologists spoke on a variety of topics: glaucoma, ocular emergencies, anesthesias used in ophthalmic surgery, and indications for vitrectomy. Members of the group spoke of the care of microinstruments, and a panel discussed preoperative, intraoperative and postoperative care of the eye patient. Approximately 100 ophthalmic nurses attended this second meeting. A. Edward Maumenee, M.D., was guest of honor at the annual luncheon meeting.

The first officers are: president, Edna Ashy, Baylor University and Veterans Administration Hospital, Houston, Texas; vice-president, Marlene Croce, Wills Eye Institute, Philadelphia; and secretary-treasurer, Corene Peacock, Johns Hopkins Hospital, Wilmer Eye Institute, Baltimore, Maryland.

The Society plans to meet at Kansas City Oct. 24 and 25, 1978, at the Ramada Central, during the American Academy of Ophthalmology meeting. Further information is available from Edna Ashy, R.N., President, American Society c Ophthalmic Registered Nurses, 27 Bellefontaine, B-33, Houston, Texa 77025.

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper, with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

CORRESPONDENCE

Metastatic Adenocarcinoma

Editor:

We read with interest the article, "Me astatic adenocarcinoma to the anteric uvea and increased carcinoembryonic ar tigen levels" (Am. J. Ophthalmol. 85:36 1978) by Gary Denslow and Richar Kielar, which described a patient wit chronic unilateral iridocyclitis, compl cated by secondary glaucoma, th masked a metastatic cancer to the anteric uveal tract. The increased plasma carc noembryonic antigen level suggested th correct diagnosis.

We have now had the opportunity t study 35 patients with metastatic canc to the choroid (Table). In ten patients th site of the primary tumor was not locate on routine clinical and laboratory exam nation. On ocular examination, the pla ma carcinoembryonic antigen level su gested the correct diagnosis in 27 patien (77%). We have also noted that whe gamma glutamyl transpeptidase, a liv enzyme, is screened carcinoembryoni antigen, with 92% of patients with met static cancer of the uvea have either a increased carcinoembryonic antigen gamma glutamyl transpeptidase level whereas routine liver enzymes may b normal, as noted in the case presented b Drs. Denslow and Kielar. Of our ten p

TABLE

CARCINOEMBRYONIC ANTIGEN LEVELS IN PATIENTS WITH OCULAR METASTASES

Primary Site	No. of Patients	Percentage of Patients with Carcinoembryonic Antigen Levels			
		0–2.5 ng/ml	2.6–5.0 ng/ml	5.l–10.0 ng/ml	>10.0 ng/ml
Breast	20	25	15	20	40
Lung	10	20	-	20	60
Gastro-intestinal	4	25	-	-	75
Adenocarcinoma of unknown site	2	-	-	-	100
All	35	22.9	5.7	17.1	54.3

tients with occult primary neoplasms, all had both increased carcinoembryonic antigen and gamma glutamyl transpeptidase levels.

As indicated in a previous study,[1] an increased level of these two enzymes may be helpful in the diagnosis of a metastatic uveal tumor from an occult primary site.

JOSEPH B. MICHELSON, M.D.
Davis, California
NORMAN J. FELBERG, PH.D.
JERRY A. SHIELDS, M.D.
Philadelphia, Pennsylvania

REFERENCE

1. Michelson, J.B., Felberg, N.T., and Shields, J.A.: Evolution of metastatic cancer to the eye. Carcinoembryonic antigen and gamma glutamyl transpeptidase. Arch. Ophthalmol. 95:692, 1977.

BOOK REVIEWS

The Pathogenesis of Nerve Damage in Glaucoma: Contributions of Fluorescein Angiography. By George L. Spaeth. New York, Grune and Stratton, 1977. Clothbound, 160 pages, table or contents, index, 64 black and white figures. $19.50

In this monograph, the author reports the comparative results of an extensive, thorough study of fluorescein angiography in glaucoma patients and normal subjects. The book is particularly valuable because of its many illustrations, the reports of illustrative individual cases, and its detailed bibliography.

The author confirms that increased intraocular pressure can cause fluorescein to proceed more slowly through the retina, choroid, and especially the optic disk. The abnormal circulation times relate to the level of pressure, and not to the presence or absence of pressure-induced damage to the disk. The angiography did not reveal why damage occurs in some people, but not in others with the pressure-induced circulatory changes.

The second major finding is the occurrence of areas of localized hypoperfusion in the disk in most cases of ordinary glaucoma and in all cases of low-tension glaucoma. From the point of view of understanding the pathogenesis of disk damage, this observation suggests three types of glaucoma: (1) hyperbaric glaucoma, in which pressure produces damage without vascular involvement, and these are the cases without areas of disk hypoperfusion despite an established visual field defect; (2) secondary ischemic glaucoma, in which the increased intraocular pressure produces vascular injury and is-

chemia with disk damage and field loss, and (3) primary ischemic glaucoma, in which vascular damage with cupping and field loss occurs without pressure (low-tension glaucoma). From the point of view of clinical usefulness, areas of hypoperfusion were seen on rare occasions before a field defect was documented. In this case, either the angiography was more sensitive than field testing in detecting early disk damage, or the angiographic findings precede and predict the occurrence of damage. Either way, angiography has potential interest. However, not all cases develop angiographic abnormalities before they develop field loss, and further work is needed to determine exactly the validity and usefulness of angiography in detecting the earliest stages of glaucomatous damage. In contrast to possible usefulness in diagnosing early disk changes, there is no evident usefulness of angiography in clearly established cases of glaucoma with field loss. The author implies that discovering areas of hypoperfusion may establish the diagnosis of low-tension glaucoma in cases where there is no explanation for a field defect, but this is difficult to conclude without showing whether other types of optic nerve disease can have areas of hypoperfusion on the disk.

The text contains interesting findings and is worthy of the attention of those interested in the details of glaucomatous optic nerve damage.

DOUGLAS R. ANDERSON

SYMPOSIA

Physiological Aspects of Clinical Neurology. Edited by F. Clifford Rose. Oxford, England, Blackwell Scientific Publications, 1977. Clothbound, 343 pages, table of contents, index, 9 tables, 197 black and white figures. $41

KENNARD, C.: **The development of binocular visual connections**

ARNOTT, E. J.: **A physiological classification of nystagmus**

SANDERS, M.D.: **Disturbances of ocular movements in cerebellar disease**

DENNY-BROWN, D.: **Spasm of visual fixation**

BENDER, MORRIS B.: **Dysfunction in the visual perception of space and motion**

ETTLINGER, G.: **Parietal cortex in visual orientation**

ROSS RUSSELL, R. W.: **Visual localization and vascular disease**

BAUMGARTNER, G.: **Neuronal mechanisms of the migrainous visual aura**

RUSHTON, D. N., AND BRINDLEY, G. S.: **Short- and long-term stability of cortical electrical phosphenes**

ECCLES, SIR JOHN: **Cerebellar function in the control of movement**

MARSDEN, C. D., MERTON, P. A., MORTON, H. B., HALLETT, M., ADAM, J., AND RUSHTON, D. N.: **Disorders of movement in cerebellar disease in man**

GRANIT, R.: **Reconsidering the "alpha-gamma" switch in cerebellar action**

WALSH, E. G.: **Persistence of stretch reflexes following cerebellar ablation--and a resonance theory of cerebellar function**

MATTHEWS, W. B.: **Familial degeneration of the cerebellum**

RICHARDSON, J. C., REWCASTLE, N. B., AND DELEAN, J.: **Hypoxic myoclonus: clinical and pathological observations**

BUCY, P. C.: **The pyramidal tract and the neural mechanism controlling voluntary movement**

RONDOT, P.: **The pathophysiology of the Parkinsonian tremor**

MENSE, S., AND SCHMIDT, R. F.: **Muscle pain: which receptors are responsible for the transmission of noxious stimuli?**

MCNAUGHTON, F. L., AND FEINDEL, W. H.: **The innervation of intracranial structures: a reappraisal**

DAMASIO, A., AND DAMASIO, H.: **Studies in dichotic listening: contributions to neurophysiology**

AIRD, R. B.: **Some observations of clinical interest on the pathophysiology of epilepsy**

SLOPER, J. C.: **Axoplasmic transport and its neuropathological implications**

Eye Movements. Edited by Barbara A. Brooks and Frank J. Bajandas. New York, Plenum Publishing Company, 1977. Hardcover, 223 pages, table of contents, foreward, references, index, 67 black and white figures. $22.50

COGAN, DAVID G.: **Enigmas and hypotheses**

ZEE, DAVID S.: **Disorders of eye-head coordination**

DELL'OSSO, LOUIS F., AND TROOST, B. TODD: **The ocular motor system. Normal and clinical studies**

ROBINSON, D. A.: **Is the cerebellum too old to learn?**

MILES, F. A.: **The primate flocculus and eye-head coordination**

COHEN, BERNARD; MATSUO, VICTOR; AND RAPHAN, THEODORE: **Optokinetic nystagmus and after-nystagmus. Characteristics and functional significance**

KELLER, EDWARD L.: **The role of the brain-stem reticular formation in eye movement control**

HIGHSTEIN, STEPHEN M.: **Abducens to medial rectus pathway in the MLF. A possible cellular basis for the syndrome of internuclear ophthalmoplegia**

BAKER, ROBERT: **The nucleus prepositus hypoglossi**

SPARKS, DAVID L., AND POLLACK, JAY G.: **The neural control of saccadic eye movements. The role of the superior colliculus**

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

American Journal of Diseases of Children

RETINOBLASTOMA AND SUBBAND DELETION OF CHROMOSOME 13. Yunis, J. J., and Ramsay, N. (Univ. of Minnesota Med. School, Minneapolis, Minn.). Am. J. Dis. Child. 132:161, 1978.

Two patients with retinoblastoma and an interstitial deletion of the long arm of chromosome 13 were studied using G-banded metaphase and prophase chromosomes. One patient showed several congenital defects, developmental retardation, and deletion of bands q14 and q21. The second patient showed mild developmental delay, a few minor congenital defects, and a loss of approximately half of band q14. On the basis of this study and nine others from the literature, it is now possible to tentatively assign a predisposition to retinoblastoma to deletion of a specific small region of chromosome 13. (2 figures, 17 references—Authors' abstract

Archives of Ophthalmology

OCULAR TOXOPLASMOSIS IN THREE CONSECUTIVE SIBLINGS. Lou, P., Kazdan, J., and Basu, P. K. (Dept. Ophthalmol., Univ. of Toronto, Toronto, Ontario). Arch. Ophthalmol. 96:613, 1978.

It is commonly believed that most retinochoroiditis seen in the general population is due to congenital toxoplasmosis. Further, since one attack is supposed to confer immunity, it seems unlikely that more than one child in a family will develop congenital ocular toxoplasmosis. This article reports such a lesion in three consecutive teenage siblings. Serologic findings were also positive. The mother was normal with normal humoral antibody levels and cell-mediated immunity. Therefore, one has to assume that either the original premise is wrong or that these three cases are in fact all acquired. (3 figures, 11 references)—David Shoch

CONGENITAL OCULAR TOXOPLASMOSIS. Stern, G. A., and Romano, P. E. (Univ. of California School of Med., San Francisco, Calif.). Arch. Ophthalmol. 96: 615, 1978.

In two siblings, the authors saw bilateral macular lesions that were consistent with the diagnosis of congenital toxoplasmosis. Although the congenital nature of this type of infection cannot be proven conclusively, there is considerable evidence that the lesions in these two young patients were scars from congenital toxoplasmic retinochoroiditis. This report and the article abstracted above appear to be the first cases of congenital ocular toxoplasmosis in siblings reported. (2 figures, 11 references)—David Shoch

INCREASED CORNEAL THICKNESS SIMULATING ELEVATED INTRAOCULAR PRESSURE. Johnson, M., Kass, M. A., Moses, R. A., and Grodzki, W. J. (Dept. Ophthalmol., Washington Univ., St. Louis, Mo.). Arch. Ophthalmol. 96:664, 1978.

A 17-year-old girl had intraocular pressure readings of 30 to 40 mm Hg in both eyes, with normal visual fields and optic nerve heads. Medical treatment was unsuccessful in lowering the intraocular pressure measurements substantially. The central corneal thickness was 0.90 mm in each eye in the absence of corneal edema. Cannulation of the left anterior chamber revealed an intraocular pressure of 11 mm Hg, while the Perkins' and Schiøtz' tonometers gave readings of 35 and 34 mm Hg, respectively. Previously, elevated tonometry readings had been obtained by Goldmann's, Perkins', Schiøtz', MacKay and Marg's, pneumatic tonometer and air puff tonometer. This suggested that measurement of central corneal thickness be performed in cases in which intraocular pressure recordings do not correspond to other clinical findings. (1 figure, 6 references)—Authors' abstract

Archives of Surgery

ASYMPTOMATIC EYEBROW MASS. Mosely, L. H., Fischer, D. S., and Polayes, I. M. (Yale Univ. School of Med., New Haven, Conn.). Arch. Surg. 113:303, 1978.

A 60-year-old woman had a solitary mass in her left eyebrow that was first thought to be a dermoid cyst and following excision and histological examination was found to be a localized, malignant, non-Hodgkin's lymphoma of the mixed lymphocytic and histiocytic type. Subsequent lymphangiography after excisional biopsy of the left eyebrow mass demonstrated extensive para-aortic and inguinal lymph node involvement. (3 figures, 10 references)—Authors' abstract

British Journal of Ophthalmology

PANRETINAL PHOTOCOAGULATION IN CENTRAL RETINAL VEIN OCCLUSION: A RANDOMIZED CONTROLLED CLINICAL STUDY. Laatikainen, L., Kohner, E.M., Khoury, D., and Blach, R. K. (Retinal Diagnostic Unit, Moorfields Eye Hosp., London). Br. J. Ophthalmol. 61:741, 1977.

The criteria for inclusion in this study were: (1) recent onset of central retinal vein occlusion (CRVO) in one eye, (2) visual acuity of 6/24 (20/80) or less, (3) no signs of neovascular glaucoma, and (4) consent to randomization. Forty-eight patients meeting these criteria were observed without treatment directed at the CRVO until three months from its estimated time of onset had elapsed, and then randomly divided into a treatment and a control group. The treatment consisted of about 400 burns of 4.5 degree spot size with the O'Malley Log II xenon arc photocoagulator, distributed evenly over the retinal area outside the temporal vascular arcade. Forty-three patients could be followed for at least one year from the time of entry into the trial. In the analysis of the results the distinction was made between two types of CRVO: an ischemic type characterized by extensive capillary closure revealed by the initial fluorescein angiogram, and a hyperpermeability type in which macular edema with profuse dye leakage dominated the angiographic picture. In the latter type the treatment had no demonstrable effect on the visual status of the eye nor on the neovascularization process and its consequences. In the treated patients with CRVO of the ischemic type neovascularization either regressed or remained stationary during the period of observation, without beneficial effect on central vision. Some peripheral vision may have been saved by the prevention of neovascular glaucoma. The authors conclude that panretinal photocoagulation should only be used in the ischemic type, and there only with the hope of preventing complications. (16 figures, 3 tables, 12 references)—Peter C. Kronfeld

ANTERIOR SEGMENT SURGERY EARLY AFTER CORNEAL WOUND REPAIR. Maul, E., and Muga, R. (Depts. Ophthalmol, Dr. Alejandro del Rio General Emergency Hosp. of Metropolitan Santiago and Universidad Calolica Med. School, Santiago, Chile). Br. J. Ophthalmol. 61:782, 1977.

After perforating injuries involving cornea and lens, complications due to swelling of the lens not infrequently occur just hours or a few days after primary surgical repair of the corneal wound. A series of 14 cases is reported to demonstrate that lens extractions by an aspiration-irrigation procedure through two small limbic keratome incisions can be performed as early as 24 hours after the first operation without disturbance of the healing process in the cornea or its ultimate clarity. (1 table, 6 references)—Peter C. Kronfeld

Laboratory Investigation

THE EFFECTS OF LEUKOCYTE DEPLETION ON CORNEAL NEOVASCULARIZATION. Sholley, M. M., Gimbrone, M. A., Jr., and Cotran, R. S. (Dept. Pathology, Peter Bent Brigham Hosp., Boston, Mass.). Lab. Invest. 38:32, 1978.

The role of leukocytic infiltration in the initiation and maintenance of corneal neovascularization was studied in rats. Vascular ingrowth was induced by central cauterization of the cornea with silver nitrate and assessed after intraarterial perfusion of colloidal carbon. In normal rats, the mean vascular length was 0.33 mm at three days and 0.63 mm at four days. Whole-body x-irradiation with 800 rads depressed peripheral blood leukocyte counts to one percent of normal, prevented infiltration of monocytes, and reduced infiltration of neutrophils, but did not alter the neovascular response at four days. Combined treatment with radiation (800 rads) and repeated injections of antineutrophil serum reduced peripheral leukocyte counts to nearly

zero and eliminated infiltration of both monocytes and neutrophils. Despite the absence of leukocytes, neovasularization occurred in all corneas. However, the mean vascular length was reduced to 67% of control at three days and to 33% at four days. The results indicate that vascular growth can be initiated in the absence of leukocytic infiltration. The reduced neovascularization in totally leukopenic animals might be due to either the ability of neutrophils to facilitate or augment vascular growth or the nonspecific effects of treatment with radiation and antineutrophil serum. (8 figures, 5 tables, 36 references)—Authors' abstract.

Mayo Clinic Proceedings

VISUAL PROGNOSIS OF OPTIC NERVE SHEATH MENINGIOMAS PRODUCING SHUNT VESSELS ON THE OPTIC DISK. Hollenhorst, R. W., Jr., Hollenhorst, R. W., Sr., and MacCarty, C. S. (Univ. of Minnesota Med. School, Minneapolis, Minn.). Mayo Clin. Proc. 53:84, 1978.

Nine patients - seven women and two men - had meningiomas of the optic nerve sheath. The defect was bilateral in two, in the right eye in six, and in the left eye in one. Most had edema of the disk, and all had progressive loss of vision in the affected eye owing to optic nerve atrophy. In ten of the 11 affected eyes, opticociliary shunt veins developed on the optic disk. Exophthalmos was mild and did not measure more than 3 mm in any patient. Ocular movement was mildly impaired in three patients. Indentation and flattening of the posterior pole of the eye were documented in five eyes. Nine of the 11 eyes progressed to blindness; one was worse after operation, and the outcome of the 11th is unknown because the patient was lost to follow-up. Surgical treatment has not been effective in these cases or in those reported in the literature. (10 figures, 22 references)—Authors' abstract

Transactions of the American Academy of Ophthalmology and Otolaryngology

THE DISK AND THE FIELD IN GLAUCOMA. Drance, S. M. (Dept. Ophthalmol., Univ. of British Columbia, Vancouver, British Columbia). Trans. Am. Acad. Ophthalmol. Otolaryngol. 85:209, 1978.

In the majority of patients who develop glaucomatous damage, early abnormalities of the disk probably precede disturbances in the visual field. An observed change in the architecture or color, or both, of the optic nerve head is certainly a reliable sign of acquired damage. The disk in advanced glaucoma is no longer capable of showing subtle changes of deterioration, and plotting of the field becomes a more reliable sign of progression of the disease. Asymmetry of the neuroretinal rim of the two optic nerves occurs rarely in the normal population. When associated with elevated intraocular pressure it should constitute strong evidence of acquired tissue change. There are 15% of cases, already with visual field defects, who cannot be reliably identified from the appearance of the disk. In such patients we are unable to recognize the appropriate features associated with these field defects, or alternately, functional loss precedes reliably recognizable disk change in them. In the majority of glaucomatous eyes, the appearance of the optic nerve head and the appearance of the visual field correlate well. Any lack of correlation between the appearance of the disk and visual field defect should redouble the search for alternative pathology to account for nerve fiber bundle damage. (16 references)—Author's abstract

THE SPECTRUM OF CHANDLER'S SYNDROME: AN OFTEN OVERLOOKED CAUSE OF UNILATERAL GLAUCOMA. Lichter, P. R. (Dept. Ophthalmol., Univ. Hosp., Ann Arbor, Mich.). Trans. Am. Acad. Ophthalmol. Otolaryngol. 85:245, 1978.

Eleven cases of unilateral glaucoma are summarized. The typical presentations of these cases are: (1) unilateral; (2) middle-aged women; (3) blurred vision; (4) corneal endothelial guttae (unilateral); (5) corneal edema; (6) stromal iris atrophy; (7) pupil abnormality; (8) peripheral anterior synechiae; (9) elevated intraocular pressure; and (10) if previously diagnosed, the diagnosis is likely incorrect. Variations in these may occur. The disease can occur in men. Some patients may have nodular iris nevi. All of them represent the spectrum of Chandler's syndrome. Accurate diagnosis is

important particularly in view of the optimistic prognostic implications for the fellow eye. (6 figures, 8 references)—Author's abstract

LONG-TERM EXPERIENCE WITH TIMOLOL OPHTHALMIC SOLUTION IN PATIENTS WITH OPEN-ANGLE GLAUCOMA. Boger, W. P., III, Puliafito, C. A., Steinert, R. F., and Langston, D. P. (Children's Hosp. Med. Ctr., Boston, Mass.). Trans. Am. Acad. Ophthalmol. Otolaryngol. 85:259, 1978.

Thirty-seven glaucoma patients used timolol ophthalmic solutions for one to 18 months. Of the 37 patients, 31 used timolol for three months or longer and seven used timolol for over one year. Timolol produced sustained reductions in intraocular pressure with continuous administration and did not induce miosis, accommodative spasm, or other annoying side effects. Systemic absorption produced a mild slowing of resting pulse rate. In some patients, timolol's ocular hypotensive effects are additive to miotics and carbonic anhydrase inhibitors. (3 tables, 22 references)—Authors' abstract

THE PATHOGENESIS OF GLAUCOMA IN STURGE-WEBER SYNDROME. Phelps, C. D. (Dept. Ophthalmol., Univ. of Iowa Hosp., Iowa City, Ia.). Trans. Am. Acad. Ophthalmol. Otolaryngol. 85:276, 1978.

Of 21 patients with Sturge-Weber disease, 16 had glaucoma. In three of the 16 the glaucoma was bilateral. Episcleral hemangiomas were visible in all glaucomatous eyes. In general, the more extensive the hemangioma, the more severe was the glaucoma. During gonioscopy, blood could easily be made to reflux into Schlemm's canal of glaucomatous eyes. Often the canal separated into multiple fine channels. Episcleral venous pressure was high in all glaucomatous eyes. These observations suggest that glaucoma in Sturge-Weber syndrome is caused by elevated episcleral venous pressure. Most likely, veins draining aqueous from the canal of Schlemm are part of an intrascleral or episcleral hemangioma. The canal of Schlemm itself may be part of the hemangioma. Arteriovenous shunts in the hemangioma raise episcleral venous pressure, which in turn elevate intraocular pressure. (4 figures, 3 tables, 18 references)—Author's abstract

ARGON LASER IRIDOTOMY IN THE TREATMENT OF PATIENTS WITH PRIMARY ANGLE-CLOSURE OR PUPILLARY BLOCK GLAUCOMA: A CLINICOPATHOLOGIC STUDY. Schwartz, L. W., Rodrigues, M. M., Spaeth, G. L., Streeten, B., and Douglas, C. (Wills Eye Hosp., Philadelphia, Pa.). Trans. Am. Acad. Ophthalmol. Otolaryngol. 85:294, 1978.

The success rate in a series of 64 patients with primary angle-closure glaucoma, treated with pulsed argon laser, was 75%. Blue eyes were slightly more difficult to penetrate. Success was almost 100% in those with pupillary block. The least successful group was patients with primary angle-closure glaucoma (58%). However, 80% penetrations were noted in the narrow-angle group. A histopathologic study including light, scanning, and transmission electron microscopy was performed on previously lasered iris tissue 12 hours to five months post-laser treatment. Edema, necrosis, pigment dispersion, and stromal disruption were noted early, while stromal atrophy and scarring were present by five months. Complications of laser iridotomy include corneal burns, pupil distortion, iritis, marked pigment dispersion, sudden rise in intraocular pressure, and retinal burns. A longer follow-up period is required before it can be stated that laser peripheral iridectomy is more advantageous than surgical peripheral iridectomy. However, the laser's simplicity and ease of administration appear to warrant its continued use at this time. (14 figures, 3 tables, 16 references)—Authors' abstract

Transactions of the Ophthalmological Societies of the United Kingdom

TRAMPOLINES AND TRIANGLES. THE SURGICAL PATHOLOGY OF THE VITREOUS. McLeon, D., and Leaver, P. K. (Moorfields Eye Hosp., London). Trans. Ophthalmol. Soc. U. K. 97:225, 1977.

The vitreous cavity may be invaded by cells penetrating through dehiscences in the inner limiting lamina of the retina, and exaggerated vitreo-retinal adhesions may also develop at such sites. The vitreous often separates from

the inner limiting lamina except at these anomalous adhesions, and retinal traction thus results from excessive movement of the otherwise detached gel; traction on the retina may also follow proliferation and contraction of invading cells on the retinal surface, along the posterior hyaloid interface, or traversing the gel. Traction complications are liable to occur at sites of vitreo-retinal adhesion during surgical removal of opaque gel, while division of transgel strands and epiretinal or posterior hyaloid membranes may be necessary in order to relieve retinal traction. (8 figures, 20 references)—Authors' abstract

RATIONALE AND TECHNIQUES OF CLOSED VITRECTOMY. Leaver, P. K., and McLeod, D. (Moorfields Eye Hosp., London). Trans. Ophthalmol. Soc. U. K. 97:242, 1977.

The three indications for vitrectomy are opacity causing severe visual deficit, vitreoretinal traction causing or threatening retinal detachment, and displacement of the vitreous from its normal position. The types of pathology which cause opacity and/or traction and which are amenable to treatment by closed vitrectomy are lens changes or lens/iris remnants, opaque vitreous gel, ochre membranes, transgel traction bands, posterior hyaloid membranes, and epiretinal membranes. Closed vitrectomy has superseded the open sky method because the integrity of the cornea is preserved, the crystalline lens can be preserved, the intraocular pressure can be regulated, and the visualization and access to the posterior segment are good. (8 figures)—Authors' abstract

EFFECT OF INTRAOCULAR LENSES ON THE CORNEAL ENDOTHELIUM. Kaufman, H. E., and Katz, J. I. (Dept. Ophthalmol., Univ. of Florida, Gainesville, Fla.). Trans. Ophthalmol. Soc. U. K. 97:265, 1977.

Methacrylate surfaces adhere to corneal endothelial cell membranes and appear to tear off the cell membranes as they separate. This adhesion appears to cause much of the massive cell damage seen at the time of intraocular lens insertion even in the hands of several groups of very experienced implant surgeons. The damage appears correlated with the incidence of endothelial touch, and may be avoidable both by avoiding contact, even for a brief period, between the endothelium and the intraocular lens during insertion, and by increasing the safety of such lenses through a hydrophilic protective coating which would give a surface similar to human lens epithelium or soft contact lens material which does not damage the endothelium. It is possible that similar damage also plays a role in causing abdominal adhesions through contact with rubber gloves, as well as venous thromboses and urethral strictures. (2 figures, 7 references)—Authors' abstract

PREVENTION OF POSTOPERATIVE OCULAR HYPERTENSION BY PROSTAGLANDIN INHIBITORS. Rich, W. J. (West of England Eye Infirmary, Exeter, England). Trans. Ophthalmol. Soc. U. K. 97:268, 1977.

The pneumatonometer of Langham was used to monitor intraocular pressure in the operating theater and in the early postoperative period after cataract surgery. Both indomethacin and aspirin were shown to produce a significant reduction in the acute ocular hypertension which can be expected to follow six hours after routine cataract surgery. It is suggested that the inhibition of prostaglandin synthesis by these drugs is probably responsible for this effect. (1 figure, 3 tables, 16 references)—Author's abstract

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.

700 North Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least three months before the date of occurrence.

XII PAN AMERICAN CONGRESS OF OPHTHALMOLOGY

The Department of Ophthalmology, Bascom Palmer Eye Institute, University School of Medicine, will sponsor the XII Pan American Congress of Ophthalmology, "Clinical Application of Recent Advances in Ophthalmic Research," at the Fontainebleau Hotel, Miami Beach, Florida, Feb. 25-March 2, 1979. Registration fees are $200 for members ($240 for nonmembers) and $110 for each accompanying person. For further information, write XII Pan American Congress of Ophthalmology, P. O. Box 610326, Miami, FL 33161.

EIGHTH CAMBRIDGE OPHTHALMOLOGICAL SYMPOSIUM

The Eighth Cambridge Ophthalmological Symposium, "Destructive Diseases of the Cornea," will be held Sept. 7 and 8, 1978, at St. John's College, Cambridge, England. For applications and further information, write Secretary, Postgraduate Medical Centre, Addenbrooke's Hospital, Hills Road, Cambridge, England.

UNIVERSITY OF CALIFORNIA, IRVINE: CORNEA AND EXTERNAL DISEASES PROGRAM

The Memorial Hospital Medical Center of Long Beach, University of California, Irvine, Center for Health Education, will hold a program, "Cornea and External Diseases," at the Center for Health Education, Long Beach, Nov. 8 and 9, 1978. For further information, write Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach, CA 90801.

NEW YORK MEDICAL COLLEGE: SEMI-ANNUAL OCULOPLASTIC SURGICAL DISSECTION COURSE

The New York Medical College Westchester County Medical Center will sponsor a semi-annual oculoplastic surgical dissection course in New York, New York, Nov. 1-4, 1978. For further information, write Mrs. P. Tamkin, c/o P. Guibor, M.D., 630 Park Ave., New York, NY 10021; telephone (212) 734-1010.

MIDWEST GLAUCOMA MEETING AND ASBURY LECTURE

The University of Cincinnati Department of Ophthalmology and Alumni Association and Cincinnati Society of Ophthalmologists and CONMED are cosponsoring the Midwest Glaucoma Meeting and Asbury Lecture at the Netherland Hilton Hotel, Cincinnati, Ohio, Nov. 9-11, 1978. For further information, call CONMED (513) 872-5486.

INTERNATIONAL SOCIETY FOR CLINICAL ELECTROPHYSIOLOGY OF VISION: 17TH SYMPOSIUM

The International Society for Clinical Electrophysiology of Vision will hold its 17th Symposium, "Visual Electrodiagnosis in Systemic Diseases," and "Visual Electrophysiology and Localized Retinal Stimulation," in Schloss Reinhardsbrunn, Friedrichroda, German Democratic Republic, June 5-10, 1979. The official language of the symposium is English. For further information, write Professor Dr. E. Schmöger, Augenklinik der Medizinische Akademie, Nordhäuserstrasse 74, 50 Erfurt, G. D. R.

EDWARD S. HARKNESS EYE INSTITUTE: NINTH ANNUAL COURSE

The Edward S. Harkness Eye Institute will present its 9th Annual Course, "Advances in Ocular Therapeutics" Nov. 16 and 17, 1978. For further information, write B. Dobli Srinivasan, M.D., Course Director, Columbia University College of Physicians and Surgeons, Department of Ophthalmology, 635 W. 165th St., New York, NY 10032.

PENNSYLVANIA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY: NEW OFFICERS

The Pennsylvania Academy of Ophthalmology and Otolaryngology announced the following officers for 1978: William C. Frayer, president; Eugene B. Rex, president-elect; James L. Curtis, first vice-president; Max L. Ronis, second vice-president; George J. Gerneth, third vice-president; Donald B. Kamerer, secretary; Donald T. Burns, secretary for instruction.

NATIONAL ADVISORY EYE COUNCIL: NEW MEMBERS

Donald S. Fredrickson, director of the National Institutes of Health announced the following new members to serve on the National Advisory Eye Council, the principal consultative body to the National Eye Institute: Kenneth T. Brown, San Francisco; Thomas D. Duane, Philadelphia, and Edward W. D. Norton, Miami. They will advise the director of the National Eye Institute, Carl Kupfer, on the awarding of grants for research and research training related to disorders of the eye and visual system, and provide guidance on program policy, planning, and development.

PERSONALS

PAUL A. COX

Paul A. Cox was awarded the Distinguished Service Award by the Pennsylvania Academy of Ophthalmology and Otolaryngology May 19, 1978. Dr. Cox was cited for his extensive service in the fields of ophthalmology and otolaryngology.

WILLIAM F. RAUB

William F. Raub has been named to serve as acting associate director for extramural research and training of the National Institutes of Health. He will serve as principal assitant and advisor to Donald S. Fredrickson, the director.

New Research Grants Awarded by the National Eye Institute

January 1, 1978-March 31, 1978

RESEARCH PROJECT GRANTS

INSTITUTION	PRINCIPAL INVESTIGATOR	TITLE OF PROJECT	COSTS AWARDED
Massachusetts Eye and Ear Infirmary Boston, Massachusetts	Daniel M. Albert	A feline model of ocular melanoma	$ 66,506
Massachusetts General Hospital Boston, Massachusetts	Adelbert Ames, III	Energy metabolism and function in retina	62,398
Colorado State University Fort Collins, Colorado	Parviz Azari	Intermolecular cross-links in lens	46,167
Medical College of Pennsylvania	Nancy E. Berman	Experimental analysis of strabismus	78,322
Emory University School of Medicine Atlanta, Georgia	Joseph C. Besharse	Studies on disk renewal in retina visual cells	67,754
University of London London, United Kingdom	Alan C. Bird	Disciform macular disease: controlled treatment trial	15,000
University of California Riverside, California	Robert R. Birge	Spectroscopy and photophysics of visual chromophores	42,665
Montefiore Hospital and Medical Center New York, New York	Margaret S. Burns-Bellhorn	Ion localization in eye physiology: new techniques	61,394
Swedish Hospital Medical Center Seattle, Washington	John W. Chandler, Jr.	Immunopathology and therapy of corneal disease	63,367
Columbia University New York, New York	D. Jackson Coleman	Therapeutic ultrasound in ophthalmology	50,969
University of California Los Angeles, California	Frederick Crescitelli	Properties of visual pigments from selected vertebrates	35,633

INSTITUTION	PRINCIPAL INVESTIGATOR	TITLE OF PROJECT	COSTS AWARDED
Harvard University Cambridge, Massachusetts	John E. Dowling	Physiology of photoreceptors of the mudpuppy retina	$42,588
University of Rochester Rochester, New York	Robert C. Emerson	Research symposium: visual deprivation	7,200
California Institute of Technology Pasadena, California	Derek H. Fender	Children's development of of reading strategies	90,465
University of Oregon Eugene, Oregon	Russell Fernald	Neural basis of visual pattern recognition in fish	86,418
Washington University University City, Missouri	James A. Ferrrendelli	Biochemistry and pharmacology of the retina	80,297
Rhode Island College Providence, Rhode Island	Neil I. Gonslaves	Eye and lens development in the anophthalmic mouse	43,855
Harvard University Boston, Massachusetts	Daniel A. Goodenough	Lens metabolic cooperation, GAP junctions & cataract	45,875
Washington University University City, Missouri	William M. Hart, Jr.	Automated digital processing of the human visual field	138,728
Ohio State University Columbus, Ohio	Richard M. Hill	The corneal environment	20,222
Eye Research Institute of Retina Foundation Boston, Massachusetts	Frank J. Holly	Investigation of tear film physiology	116,561
Medical College of Georgia Augusta, Georgia	David S. Hull	Drugs, pathologic conditions and cornea endothelium	23,468
Eye Research Institute of Retina Foundation Boston, Massachusetts	Erwin Hultsch	Chemistry and morphology of vitreous regeneration	94,758
University of California San Francisco, California	Regis B. Kelly	Proteins of the mammalian visual system	62,526
University of Texas Galveston, Texas	Arthur Koblasz	Nonlinear analysis of the human electroretinogram	9,990
Rensselaer Polytechnic Institute Troy, New York	Jane F. Koretz	A computer model for lens accomodation	16,604
New York University New York, New York	David L. Krohn	Transcorneal flux enhancement of pilocarpine	98,715
Boston Biomedical Research Institute Boston, Massachusetts	Sherwin S. Lehrer	Intraocular muscle-biochemical studies	38,519
University of California Davis, California	Alan D. MacMillan	Familial dystrophic and dysplastic eye diseases of dogs	12,839

INSTITUTION	PRINCIPAL INVESTIGATOR	TITLE OF PROJECT	COSTS AWARDED
University of Florida Gainesville, Florida	Thomas H. Maren	New approaches to glaucoma and lens pharmacology	$133,907
University of Texas Dallas, Texas	John M. Martinez, III	Colorimetric analysis of glaucoma	72,816
Stanford University Stanford, California	James P. Mc Culley	Meibomian keratoconjunctivitis	85,672
State University of New York Buffalo, New York	Robert F. Miller	Cell communication in the vertebrate retina	95,480
University of California Berkeley, California	Sheldon S. Miller	Homeostatic ability of the retinal pigment epithelium	79,985
Estelline Community Hospital Estelline, South Dakota	Donald S. Mincklep	Morphology of monkey optic nerve	92,684
University of British Columbia Vancouver, Canada	Robert S. Molday	A study of retinal photo-receptor membrane proteins	30,000
University of California La Jolla, California	S. Mauricio Montal	Rhodopsin in bilayer membranes and visual excitation	135,871
University of Michigan Ann Arbor, Michigan	Richard G. Northcutt	Anatomical and behavioral organization	53,449
University of California Riverside, California	William H. Okamura	Studies on the retinoids and vinyl allene chemistry	17,460
State University New York Stony Brook, New York	William G. Owen	Signal transfer between receptors and bipolar cells	86,998
Mount Sinai School of Medicine New York, New York	Tauba Pasik	Maturation of monkey and basal ganglia systems	80,744
Rockefeller University New York, New York	Barry W. Peterson	Properties of premotor neurons in gaze control system	64,323
Wayne State University Detroit, Michigan	Howard Rothstein	Hormonal control of lens growth	116,224
University of Southern California Los Angeles, California	Stephen J. Ryan	Pars plana vitrectomy in penetrating ocular trauma	124,998
University of Chicago Chicago, Illinois	Eric A. Schwartz	Development of photo-receptors in a vertebrate eye	88,892
Chicago State University Chicago, Illinois	Warren V. Sherman	Light response of the purple membrane of *H. halobium*	55,229
New York University New York, New York	Irwin M. Siegel	Electrical analysis of receptor in retinal dystrophy	133,635
Northeastern University Boston, Massachusetts	Alexander A. Skavenski	Eye movement and mechanisms of visual localization	55,239
University of Washington Seattle, Washington	Charles E. Stirling	Retinal transport mechanisms	36,274

INSTITUTION	PRINCIPAL INVESTIGATOR	TITLE OF PROJECT	COSTS AWARDED
Stanford University Stanford, California	Lubert Stryer	Time-resolved resonance raman studies of vision	$112,620
University of Illinois Medical Center Chicago, Illinois	Joel Sugar	Trigger mechanisms of recurrent herpes keratitis	35,301
Johns Hopkins University Baltimore, Maryland	Tung-Tien Sun	Studies of corneal epithelial differentiation	116,676
Massachusetts Institute of Technology Cambridge, Massachusetts	Toyoichi Tanaka	Quantitative characterization of lens opacities	73,813
Kirksville College of Osteopathic Medicine Kirksville, Missouri	Lex C. Towns	Anatomical interconnections of rabbit visual system	31,561
St. Marianna University Kawasaki, Japan	June-Ichi Toyoda	Ionic basis of retinal cell potential	19,560
University of Maryland Baltimore, Maryland	Shambhu D. Varma	Aldose reductase in ocular pathology	65,905
University of California Davis, California	George O. Waring, III	Animal models of corneal dystrophies and degenerations	52,335
Florida State University Tallahassee, Florida	Theodore P. Williams	Damaging effects of visible light	66,286
University of California Los Angeles, California	Richard W. Young	Daily rhythms in visual cell metabolism	38,126

CORE CENTER GRANTS AND SPECIALIZED CLINICAL RESEARCH CENTER GRANTS

University of Miami Miami, Florida	Douglas R. Anderson	Ophthalmic research core facility	$284,059
New York University New York, New York	Ronald E. Carr	Clinical center for hereditary retinal degenerations	83,754

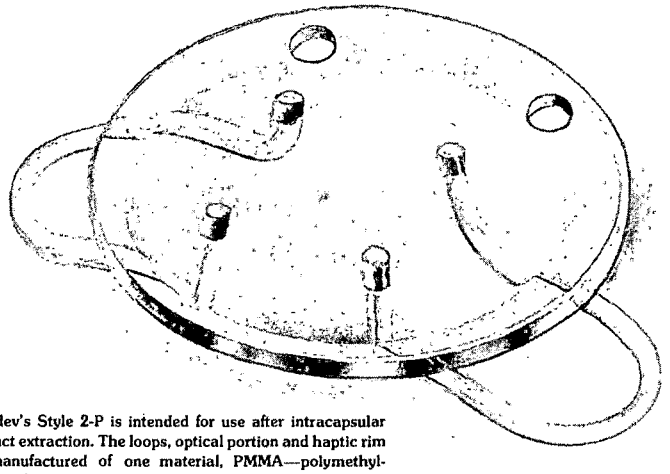
NATIONAL RESEARCH SERVICE AWARD FELLOWSHIPS

University of Pennsylvania Philadelphia, Pennsylvania	Gregory M. Acland	Retinal degeneration and phosphodiesterase inhibitors	$13,200
U.S. Department of Defense Washington, D.C.	Mary C. Bushnell	Visually responsive neurons in parietal cortex	10,387
University of California San Francisco, California	Steven E. Feldon	Eye movement disorders	12,800
University of Iowa Iowa City	Jonathan D. Fratkin	Properties of cells isolated from retinal microvessels	13,200
University of Wisconsin Madison, Wisconsin	Eldon E. Geisert, Jr.	A study of monocular deprivation in cats	10,000

INSTITUTION	PRINCIPAL INVESTIGATOR	TITLE OF PROJECT	COSTS AWARDED
Massachusetts Institute of Technology Cambridge, Massachusetts	Thomas P. Langer	Visual-oculomotor processing in superior colliculus	$10,800
Johns Hopkins University Baltimore, Maryland	Richard J. Leigh	Adaptive mechanisms to maintain ocular motor balance	13,200
Massachusetts Institute of Technology Cambridge, Massachusetts	Harris R. Lieberman	Basic and applied visual psychophysical research	10,800
College of Medicine and Dentistry of New Jersey Newark, New Jersey	Annette B. Mears	Studies in cataract reversal	10,000
Johns Hopkins University Baltimore, Maryland	Brad C. Mottor	Parietal lobe mechanisms in selective visual attention	10,000
Dalhousie University Halifax, Canada	Michael J. Mustari	Binocular interaction in visual cortex	10,800
U.S. Alcohol, Drug Abuse and Mental Health Administration Rockville, Maryland	Lance M. Optican	Cerebellar control of saccadic eye movements	10,000
Massachusetts General Hospital Boston, Massachusetts	Glen A. Pu	Neurotransmitters in the IPL of the retina	10,000
University of Michigan Ann Arbor, Michigan	Anne C. Rusoff	Anatomical development of the goldfish visual system	10,000
Harvard University Boston, Massachusetts	Stephen M. Sager	Inhibition in the mammalian visual system	13,200
U.S. National Institutes of Health Bethesda, Maryland	Julie L. Schnapf	Voltage-dependent light adaptation in photoreceptors	10,387
Harvard University Boston, Massachusetts	Helen A. Sherk	Monocular deprivation and visual cortex changes	10,000
University of Wisconsin Madison, Wisconsin	Lillian Tong	Effects of visual deprivation on LS cortex in cat	10,000
University of Florida Gainesville, Florida	Leslie W. Williams	Veterinary ophthalmology: primary glaucoma in beagles	13,200
RESEARCH CAREER DEVELOPMENT AWARDS AND ACADEMIC INVESTIGATOR AWARDS			
Montefiore Hospital and Medical Center New York, New York	Margaret B. Bellhorn	Ion localization in eye physiology: new techniques	$39,888
University of California San Francisco, California	Devon H. Char	Uveitis and eye tumors: immunodiagnosis and monitoring	39,204
Children's Hospital Medical center Boston, Massachusetts	Anne B. Fulton	Signal processing in normal and abnormal retina	34,250

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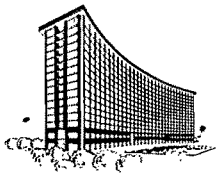
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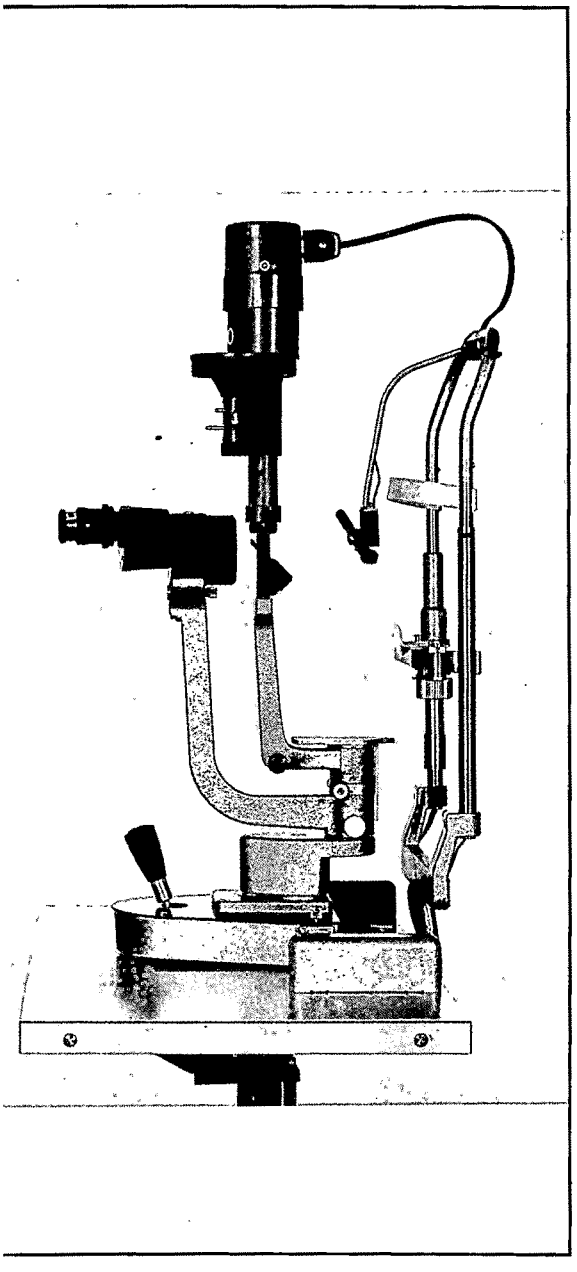


Anyone interested in presenting original papers, movies, scientific or technical exhibits, is requested to submit his interest to the Symposium Chairman by October 15, 1978.

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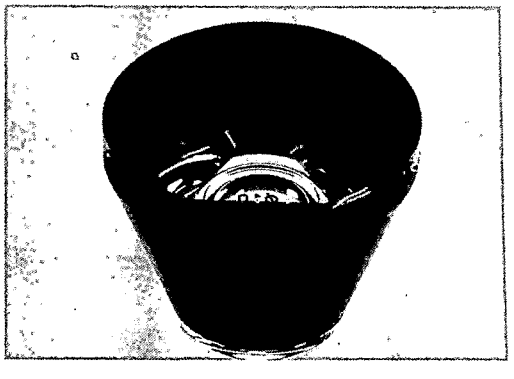
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Warnings: 1. *Use in Pregnancy:* Safe use of anticholinesterase medications during pregnancy has not been established, nor has the absence of adverse effects on the fetus or on the respiration of the neonate.

2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patients receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.

3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same time undergoing treatment with systemic anticholinesterase medications for myasthenia gravis, because of possible adverse additive effects.

Precautions: 1. Gonioscopy is recommended prior to initiation of therapy.

2. Where there is a quiescent uveitis or a history of this condition, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.

3. While systemic effects are infrequent, proper use of the drug requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into the nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.

4. Temporary discontinuance of medication is necessary if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregularities occur.

5. Patients receiving PHOSPHOLINE IODIDE who are exposed to carbamate or organophosphate type insecticides and pesticides (professional gardeners, farmers, workers in plants manufacturing or formulating such products, etc.) should be warned of the additive systemic effects possible from absorption of the pesticide through the respiratory tract or skin. During periods of exposure to such pesticides, the wearing of respiratory masks, and frequent washing and clothing changes may be advisable.

6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects.

7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.

8. PHOSPHOLINE IODIDE (echothiophate iodide) should be used with great caution, if at all, where there is a prior history of retinal detachment.

Adverse Reactions: 1. Although the relationship, if any, of retina detachment to the administration of PHOSPHOLINE IODIDE has not been established, retinal detachment has been reported in a few cases during the use of PHOSPHOLINE IODIDE in adu patients without a previous history of this disorder.

2. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.

3. Activation of latent iritis or uveitis may occur.

4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.

5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.

6. Lens opacities occurring in patients under treatment for glaucoma with PHOSPHOLINE IODIDE have been reported, and similar changes have been produced experimentally in normal monkeys. Routine examinations should accompany clinical use of the drug.

7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.

Overdosage: Antidotes are atropine, 2 mg parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg per k intravenously; artificial respiration should be given if necessary.

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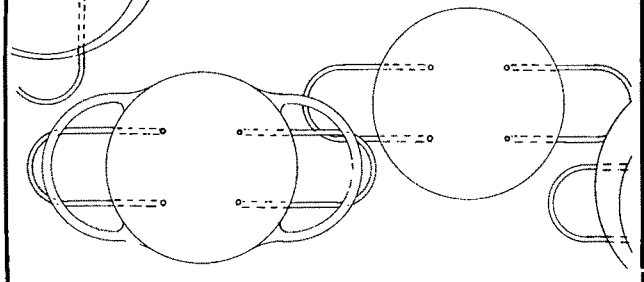
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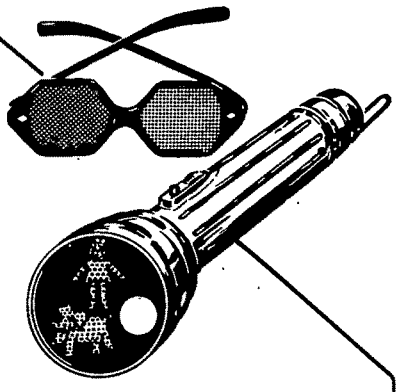
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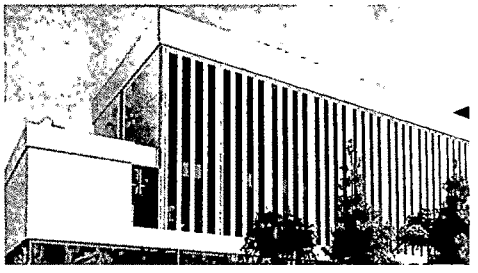


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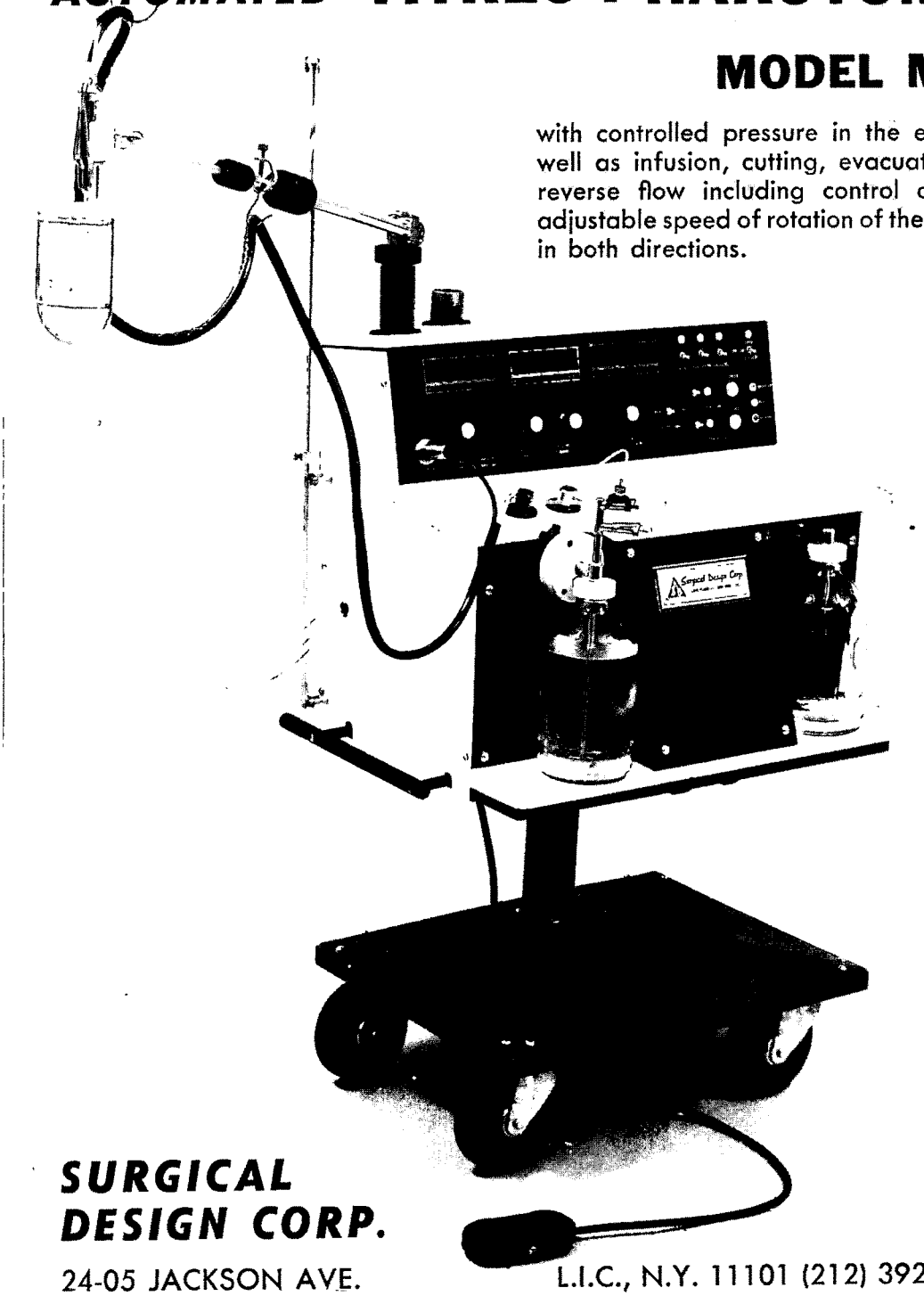
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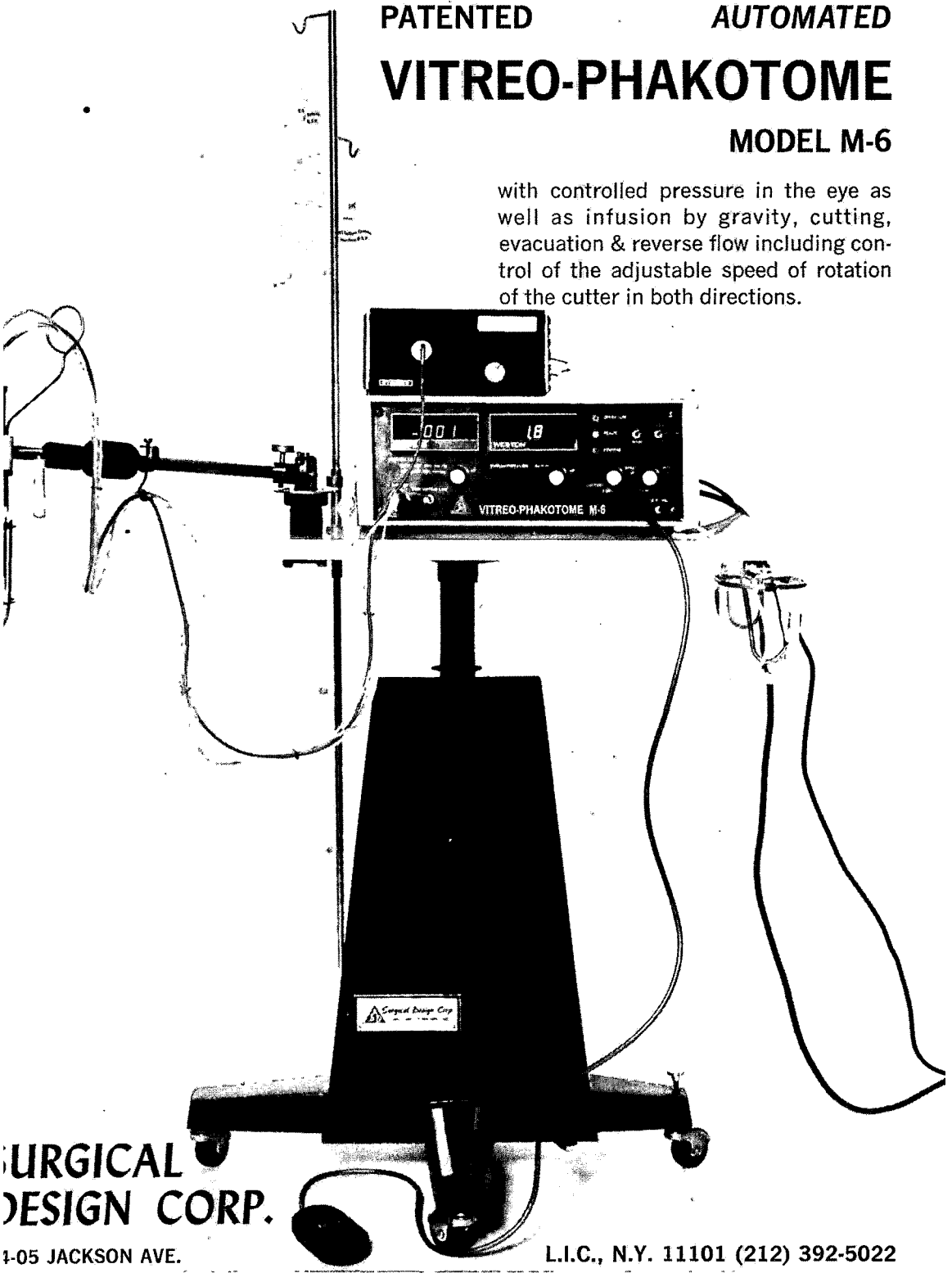
Vitreous Surgery: Arch. Ophthalmol.
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Provisional programme

Monday morning: Subjects covered—Lens/cornea. Cornelius Binkhorst (Terneuzen)—Lens implant surgery; Gunther Mackensen (Freiburg)—Corneal surgery; Jan Worst (Groningen)—Anterior Segment Lens; and others.

Monday afternoon: Subjects covered—Medical Retina/choroid. Alan Bird (London)—Treatment of senile disciform macular degeneration, Axoplasmic flow; Pierre Amalric (Albi)—Choroidal vascularization; Jean Jacques De Laey (Gent)—Fluoresceine Angiography; Donald Gass (Miami)—Ocular tumors, Macular diseases; Karl Ossoing (Iowa)—Ultrasound in Ophthalmology.

Tuesday morning: Subjects covered—Surgical retina. Lorimer Fison (London)—Retinal detachment; Gerd Meyer Schwickenrath (Essen)—Laser and versus Xenon; Dennis Robertson (Rochester)—Central serous retinopathy and treatment; Achim Wessing (Essen)—Fluoresceine Angiography; Edward Norton and others.

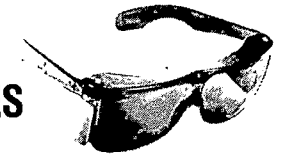
Tuesday afternoon: Subjects covered—Vitreous surgery/trauma diabetes. Rudolf Kloti (Zurich)—Vitrectomy; Ronald Michels (Baltimore)—Diabetes and vitrectomy; Steven Ryan (Los Angeles)—Trauma and vitrectomy; Jules Francois (Gent)-Proliferation of lens epithelium; Edward Norton (Miami)—Vitrectomy—past, present and future; Karl Ossoing and others.

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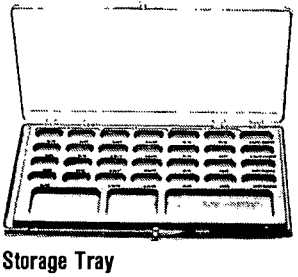
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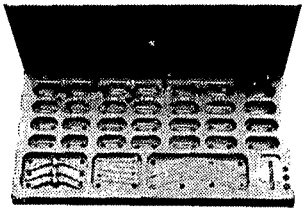
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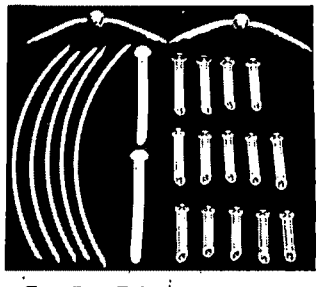
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* L.T. Jones M.D., Dacryocystorhinostomy, American Journal of Ophthalmology, Volume 59, No. 5, May, 1965.
J.C. Mustarde', L.T. Jones M.D. and A. Callahan M.D., Ophthalmic Plastic Surgery---Up-To-Date, Aesculapius Publishing Company, 1970.
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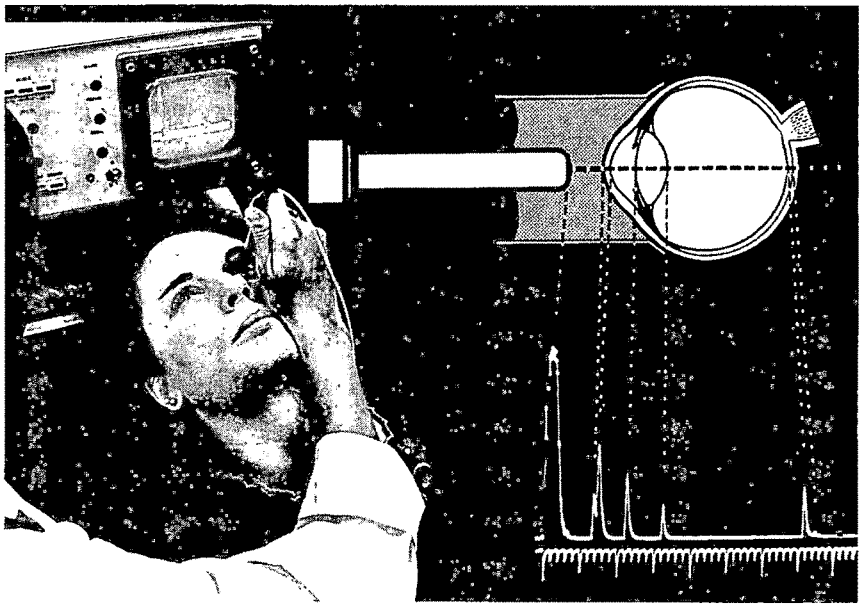
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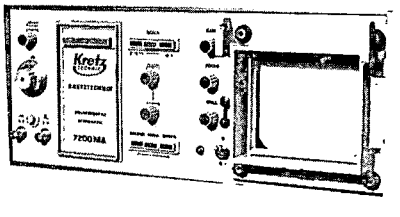


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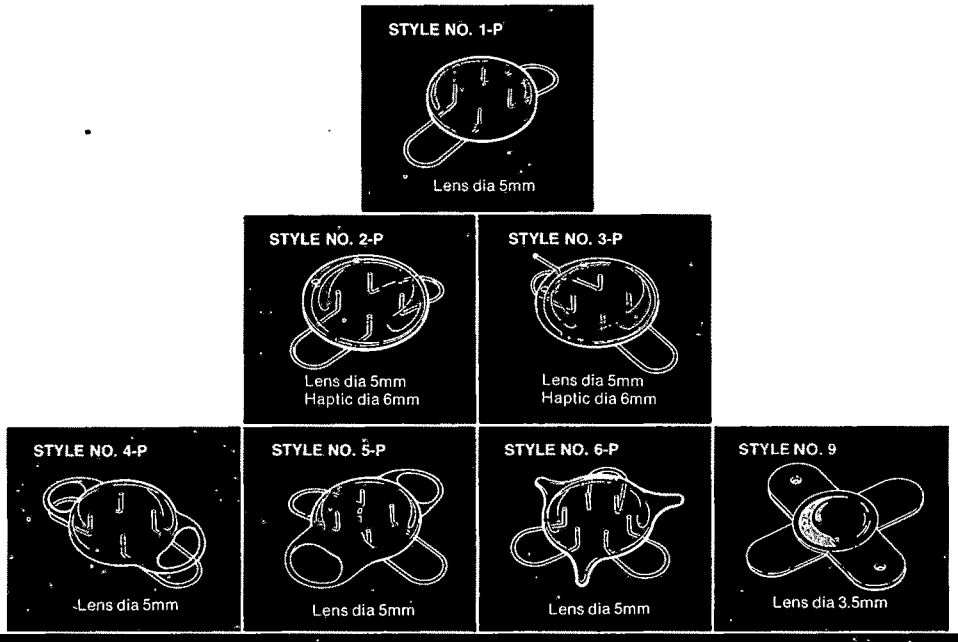
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REFERENCE NOTES:

1. Allergan Report Series, #72.
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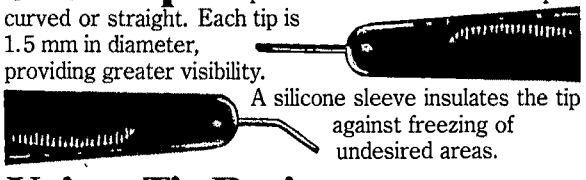
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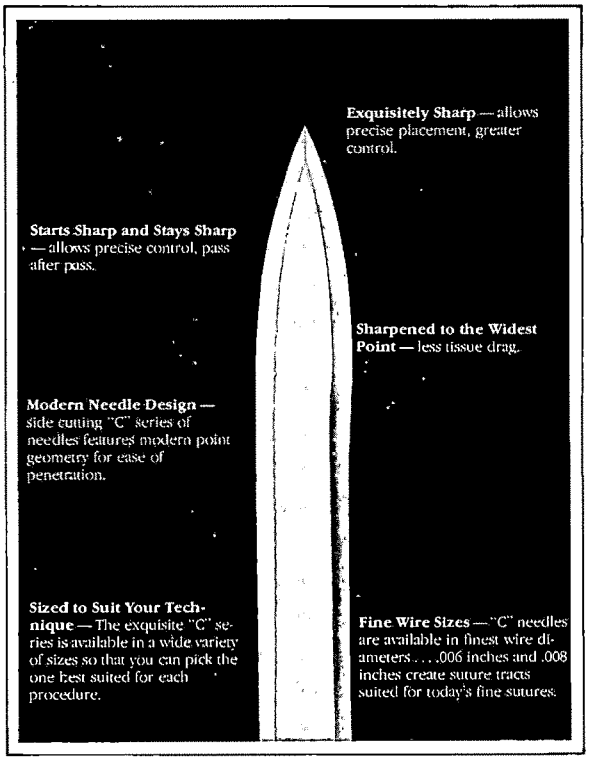
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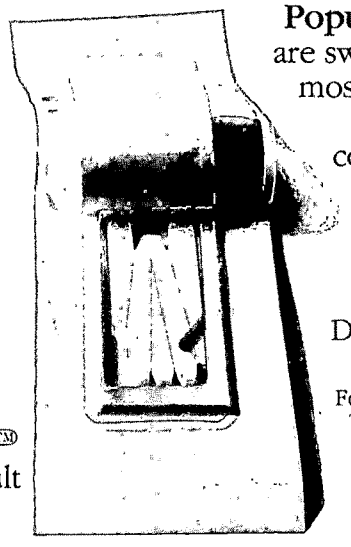


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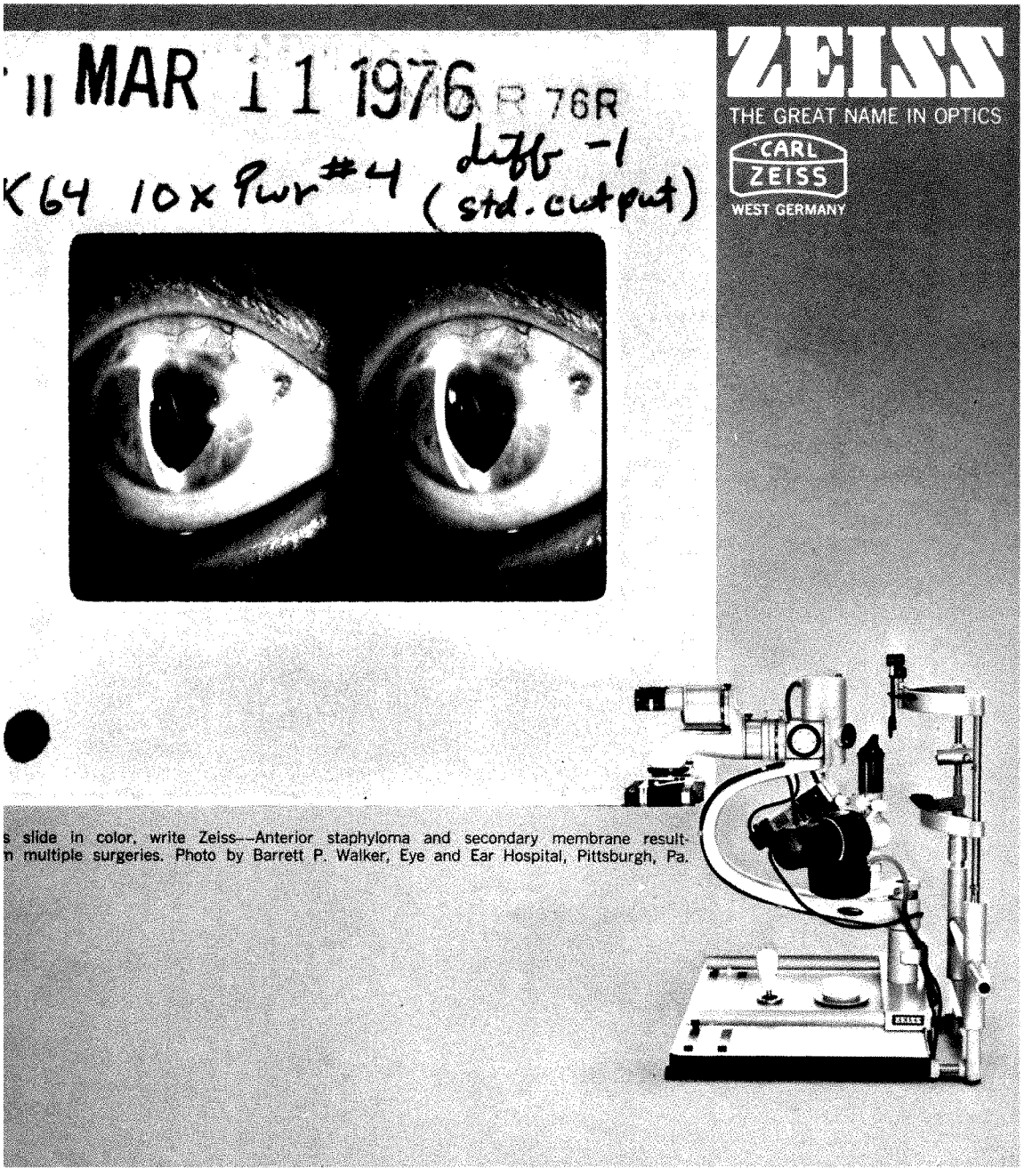
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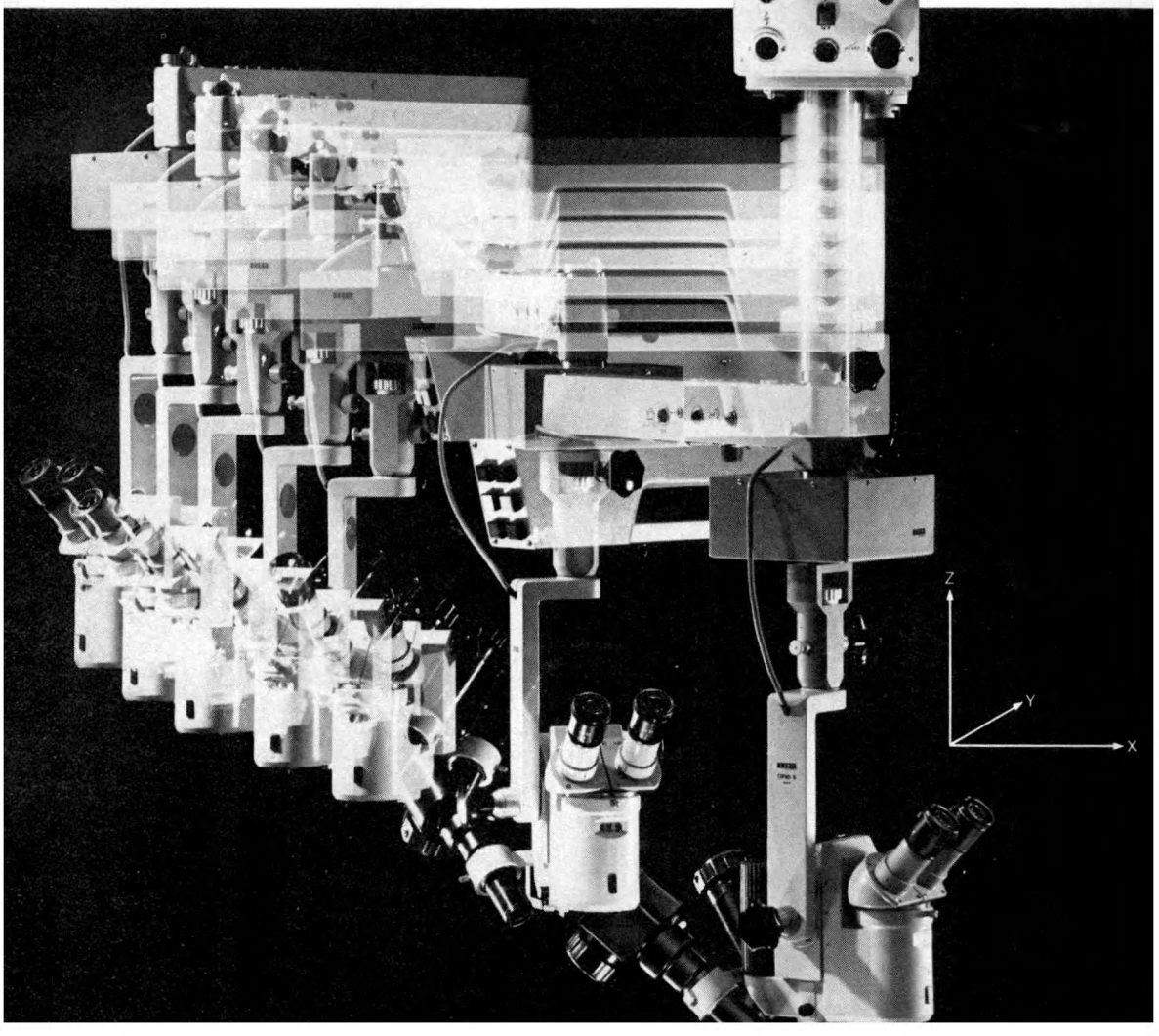
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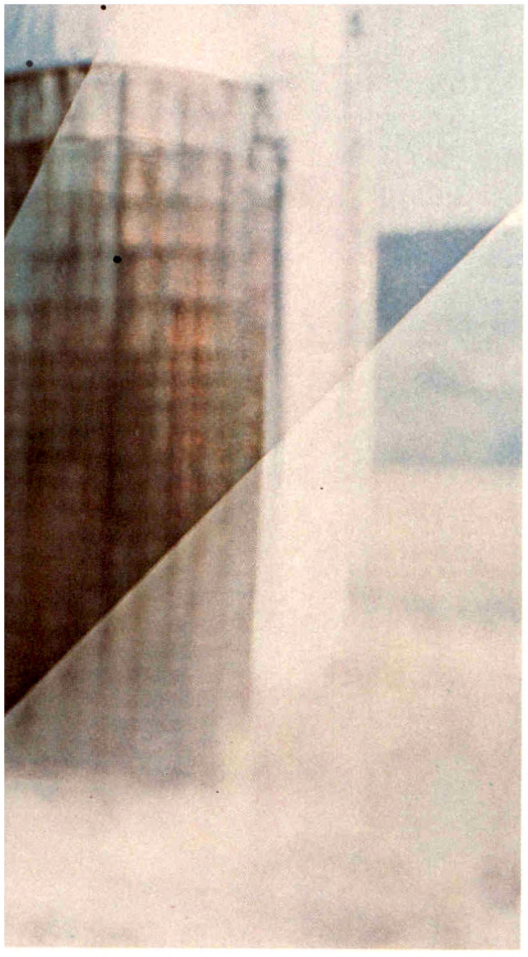
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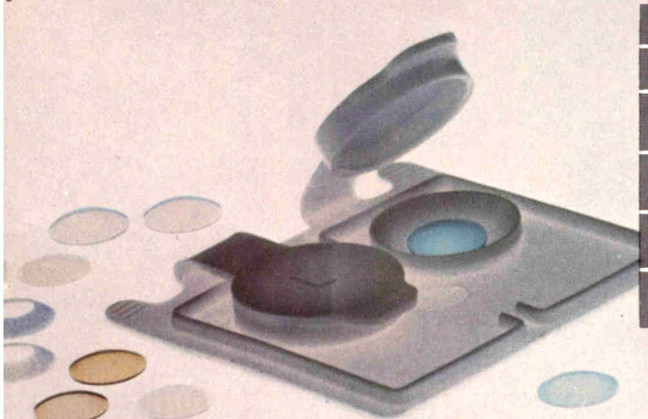
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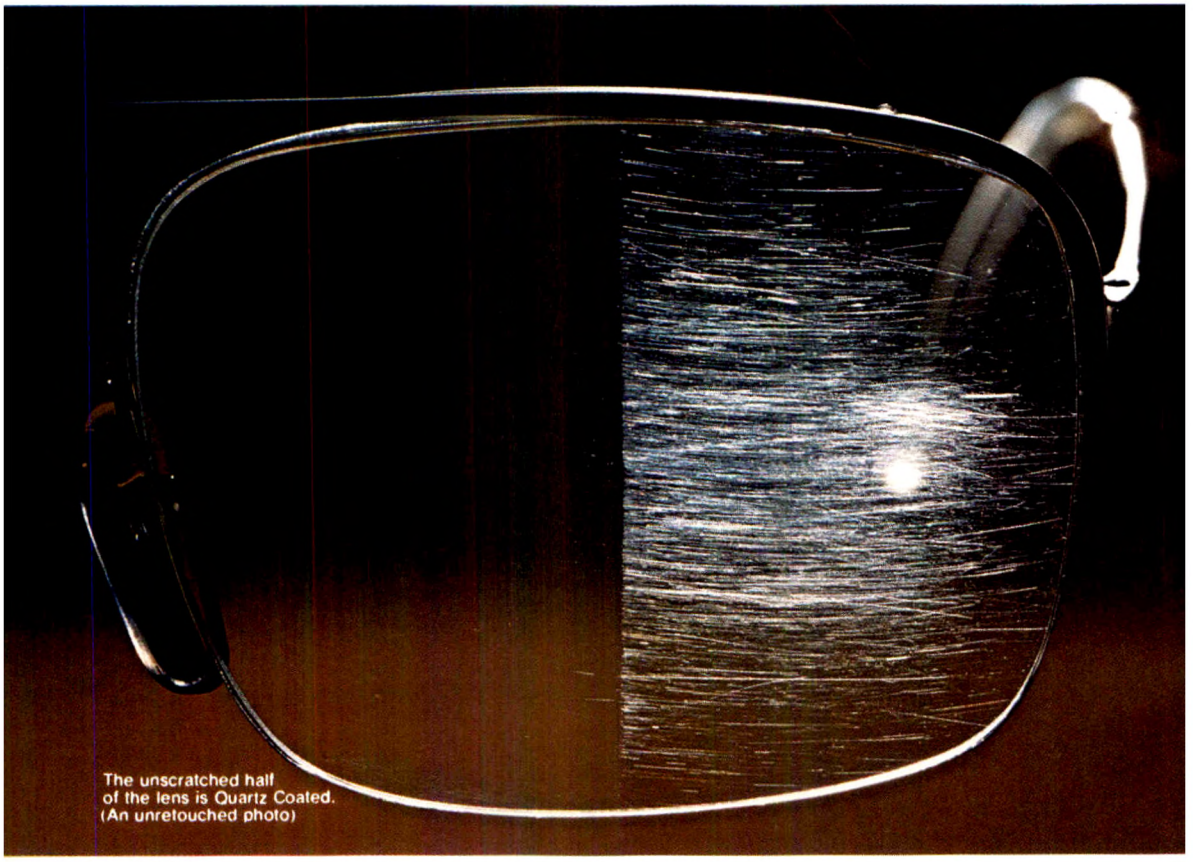
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As an easy guide, the following types of resin lenses can be coated with Hi-Quartz: Single Vision: Flat Top 22, 25, 28; Round 22. These types of resi lenses cannot be coated with Hi-Quartz: Trifocal and Executive.

Finally, Hi-Quartz has all the advantages of ordinary resin lenses, including safety, lightness and ability to be dyed. (Dyeing must be done before the quartz coating takes place.)

HOYA's Hi-Quartz lens. When it comes to quality products HOYA hasn't even begun tc scratch the surface.

*HOYA cannot accept cut or uncut lenses sent into the Torrance full prescription laboratory due to possible lens imperfections that could interfere with the quartz.

HOYA LENS OF AMERICA, INC.

To place your order, call or write: HOYA LENS OF AMERICA, INC., 970 Knox Street, Torrance, CA. 90502
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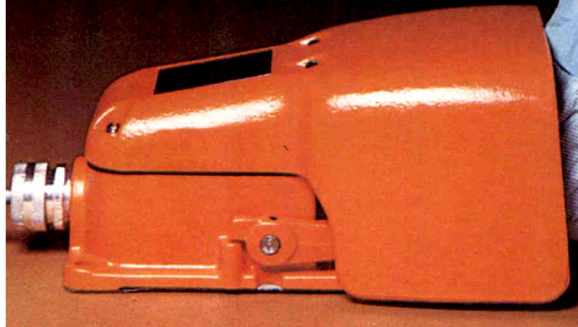
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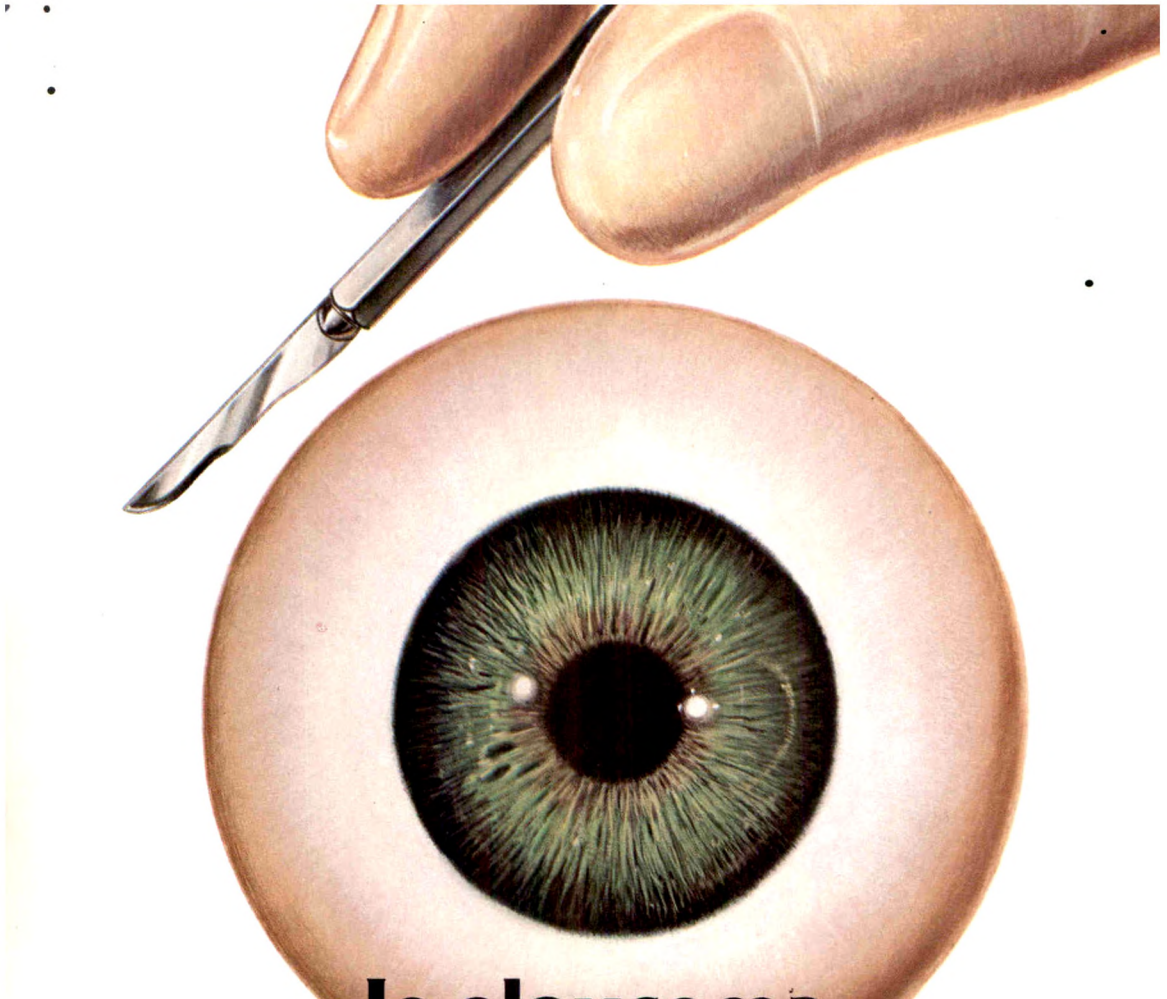
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In glaucoma, the last step before surgery

When chronic glaucoma becomes refractory to acetazolamide and miotics, consider NEPTAZANE before resorting to surgery. A significant number of patients no longer responding to acetazolamide have been controlled by methazolamide.[1] There are differences, too, when it comes to side effects, since many patients intolerant to acetazolamide may be maintained on methazolamide. So whether the problem is inadequate I.O.P. control or drug intolerance, NEPTAZANE is worth a trial before surgery.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: For adjunctive treatment of chronic simple (open angle) glaucoma, secondary glaucoma, and preoperatively in acute angle closure glaucoma where delay of surgery is desired in order to lower intraocular pressure.

Contraindications: Severe or absolute glaucoma and chronic noncongestive angle closure glaucoma. Of doubtful use in glaucoma due to severe peripheral anterior synechiae or hemorrhagic glaucoma. Adrenocortical, hepatic, or renal insufficiency; electrolyte imbalance state, e.g., hyperchloremic acidosis; sodium and potassium depletion states.

Warnings: Although teratogenic effects demonstrated in rats at high doses have not been evidenced in humans, Methazolamide should not be used in women of childbearing potential or in pregnancy, especially in the first trimester, unless the expected benefits outweigh potential adverse effects.

Precautions: Use with caution in patients with cirrhosis or hepatic insufficiency to forestall hepatic coma; those on steroid therapy; those with pulmonary obstruction or emphysema to avoid acidosis. Electrolyte balance should be maintained. Although not reported thus far with this drug, reactions common to sulfonamide derivatives, such as fever, leukopenia, hemolytic anemia, bone marrow depression or renal calculi, may occur.

Adverse Reactions (relatively mild and disappear on withdrawal or dosage adjustment): anorexia, nausea, vomiting; malaise, fatigue or drowsiness, headache; vertigo, mental confusion, depression, paresthesias. Urinary citrate excretion and uric acid output is decreased during use of this drug, but urinary calculi have not been reported.

NEPTAZANE®
METHAZOLAMIDE Tablets 50 mg.

Lederle LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York 10965

[1] Havener, WH. Ocular Pharmacology. Third Ed. The C. V. Mosby Co., St. Louis, 1974, pg. 478.

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Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indication: Herpes simplex keratitis (topical use only).

Contraindications: Known or suspected hypersensitivity to any of the components.

Warning: Administer with caution in pregnancy or women of childbearing potential. Malformations were reported in one study in rabbits when idoxuridine was instilled in the eyes of the dams; a subsequent, more detailed study in rabbits showed no such effects, even at substantially higher dosages.

Precautions: If there is no response in epithelial infections after 7 or 8 days, other therapy should be considered. Recommended frequency and duration of administration should not be exceeded. Not effective in corneal inflammations if herpes simplex is not present. Boric acid should not be used concomitantly. To insure stability is maintained, the solution should not be mixed with other medications.

Adverse reactions: Occasionally, irritation, pain, pruritus, inflammation, or edema of the eye or lid; rarely, allergic reactions have been reported. Photophobia has occurred. Occasionally, small punctate defects (which may be a manifestation of the infection), corneal clouding, and stippling of the corneal epithelium have been observed.

Supplied: 0.1% Ophthalmic Solution (1 mg./ml.) in 15 ml. bottles with dropper; 0.5% Ophthalmic Ointment (5 mg./gram) in 4 gram tubes.

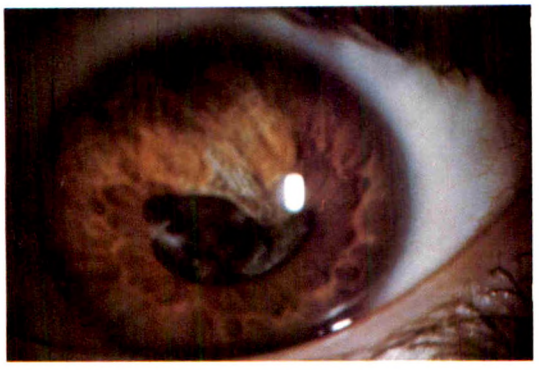
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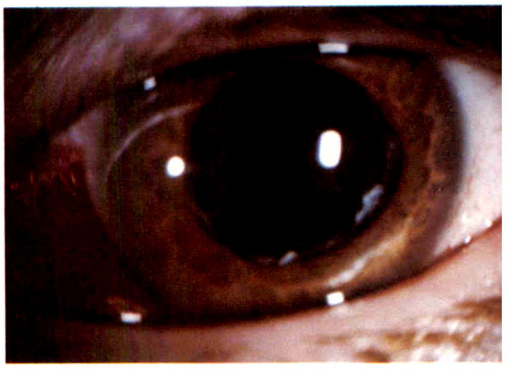
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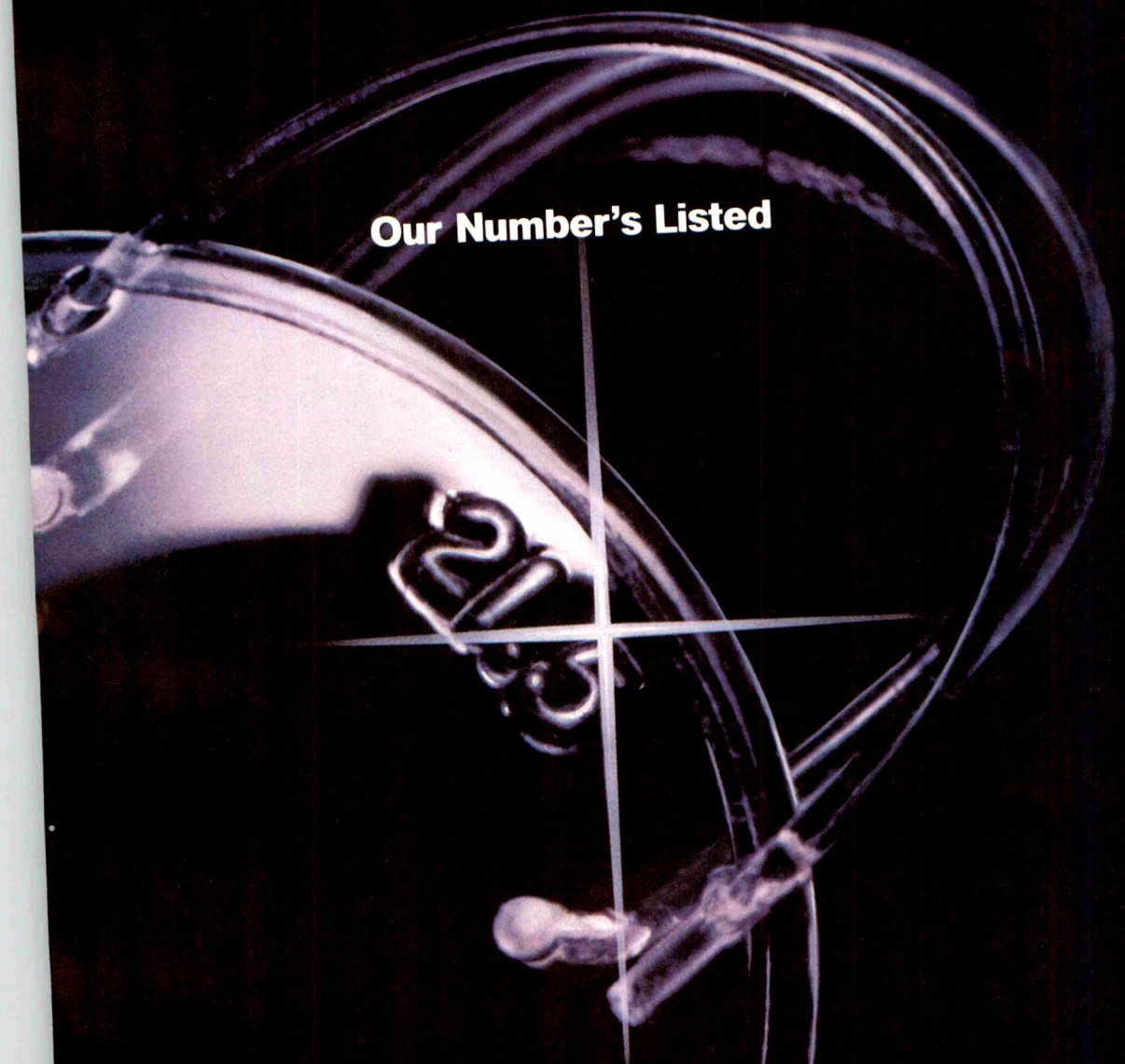
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gentamicin sulfate, U.S.P.
OPHTHALMIC
Solution-Sterile
Ointment-Sterile

Each ml. or gram contains gentamicin sulfate equivalent to 3.0 mg. gentamicin.

DESCRIPTION Gentamicin sulfate is a water-soluble antibiotic of the aminoglycoside group active against a wide variety of pathogenic gram-negative and gram-positive bacteria.

GARAMYCIN **Ophthalmic Solution** is a sterile, aqueous solution buffered to approximately pH 7 for use in the eye. Each ml. contains gentamicin sulfate (equivalent to 3.0 mg. gentamicin), disodium phosphate, monosodium phosphate, sodium chloride, and benzalkonium chloride as a preservative.

GARAMYCIN **Ophthalmic Ointment** is a sterile ointment each gram containing gentamicin sulfate (equivalent to 3.0 mg. gentamicin) in a bland base of white petrolatum, with methylparaben and propylparaben as preservatives.

ACTIONS The gram-positive bacteria against which gentamicin sulfate is active include coagulase-positive and coagulase-negative staphylococci, including certain strains that are resistant to penicillin; Group A beta-hemolytic and nonhemolytic streptococci; and *Diplococcus pneumoniae*. The gram-negative bacteria against which gentamicin sulfate is active include certain strains of *Pseudomonas aeruginosa*, indole-positive and indole-negative *Proteus* species, *Escherichia coli*, *Klebsiella pneumoniae* (Friedlander's bacillus), *Haemophilus influenzae* and *Haemophilus aegyptius* (Koch-Weeks bacillus), *Aerobacter aerogenes*, *Moraxella lacunata* (diplobacillus of Morax-Axenfeld), and *Neisseria* species including *Neisseria gonorrhoeae*. Although significant resistant organisms have not been isolated from patients treated with gentamicin at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.

INDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are indicated in the topical treatment of infections of the external eye and its adnexa caused by susceptible bacteria. Such infections embrace conjunctivitis, keratitis and keratoconjunctivitis, corneal ulcers, blepharitis and blepharoconjunctivitis, acute meibomianitis, and dacryocystitis.

CONTRAINDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are contraindicated in patients with known hypersensitivity to any of the components.

WARNINGS GARAMYCIN **Ophthalmic Solution** is not for injection. It should never be injected subconjunctivally, nor should it be directly introduced into the anterior chamber of the eye.

PRECAUTIONS Prolonged use of topical antibiotics may give rise to overgrowth of nonsusceptible organisms, such as fungi. Should this occur, or if irritation or hypersensitivity to any component of the drug develops, discontinue use of the preparation and institute appropriate therapy.

Ophthalmic ointments may retard corneal healing.

ADVERSE REACTIONS Transient irritation has been reported with the use of GARAMYCIN **Ophthalmic Solution.**

Occasional burning or stinging may occur with the use of GARAMYCIN **Ophthalmic Ointment.**

DOSAGE AND ADMINISTRATION GARAMYCIN **Ophthalmic Solution:** instill one or two drops into the affected eye every four hours. In severe infections, dosage may be increased to as much as two drops once every hour.

GARAMYCIN **Ophthalmic Ointment:** apply a small amount to the affected eye two to three times a day.

HOW SUPPLIED GARAMYCIN **Ophthalmic Solution—Sterile,** 5-ml. plastic dropper bottle, sterile; boxes of one and six. Store away from heat.

GARAMYCIN **Ophthalmic Ointment—Sterile,** ⅛-ounce tube; boxes of one and six. Store away from heat.

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For complete details, consult package insert or literature available from your Schering Representative, or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

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Gram-positive: susceptible strains of: staphylococci and streptococci, including *D. pneumoniae.*

Problem pathogens: susceptible strains of: *P. aeruginosa* and *Proteus* sp. (indole-positive and -negative).

for gentle potency—generally avoids sensitivity reactions and irritation.

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broad spectrum activity against many gram-negative and gram-positive organisms

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brand of
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each ml. or gram contains gentamicin sulfate equivalent to 3.0 mg. gentamicin.

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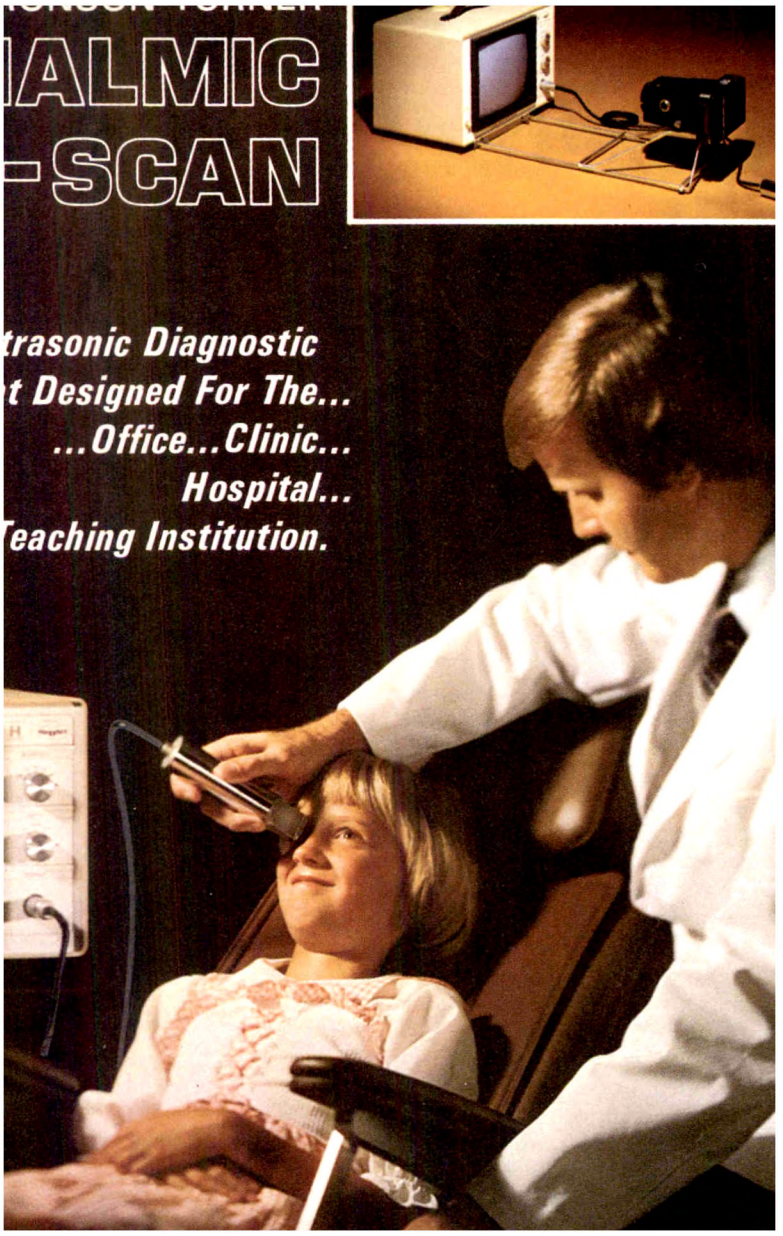
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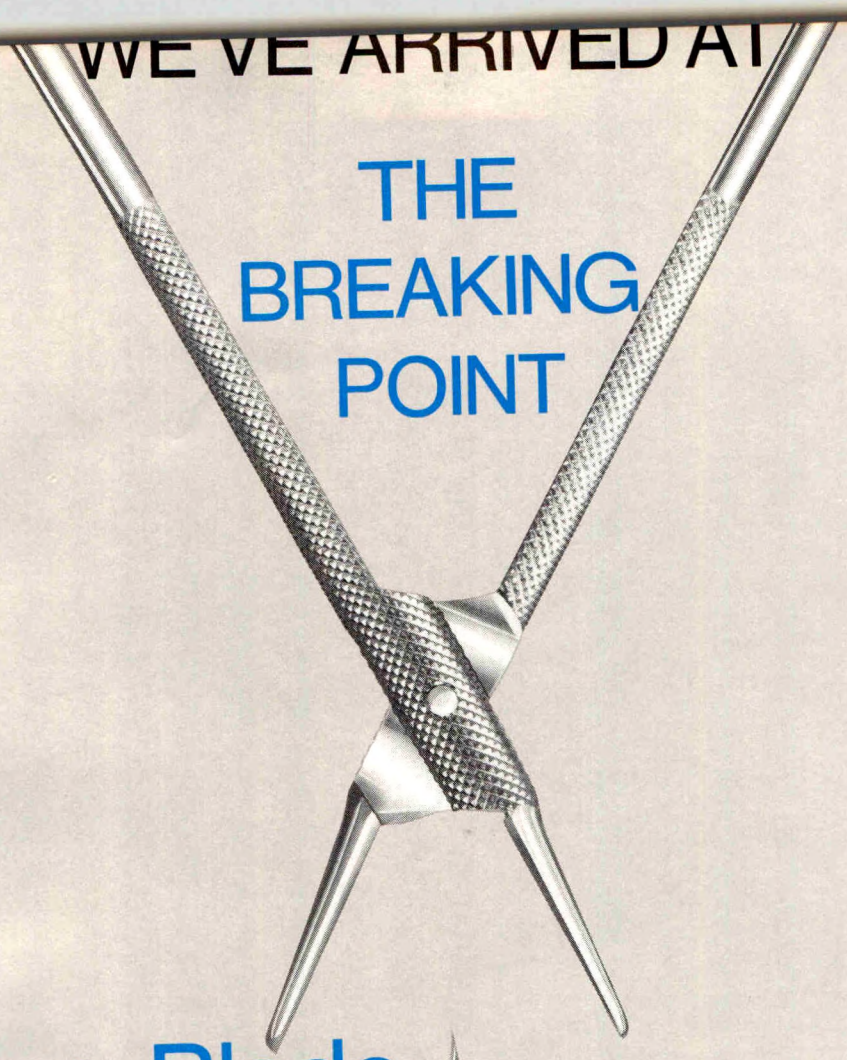
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Your patients can expect comfort from the first day you fit them, with a minimum of spectacle blur. You get few patient "call-backs" since problems are minimal with the rapid adaptation and easy-to-wear schedule of the AOSOFT lens.

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Now you can spend your valuable time on more important things. You can increase your practice income potential, make your practice more cost-efficient, increase your patient flow. Today, thousands of your colleagues are enjoying less complicated practices by building on the AOSOFT lens, the uncomplicated soft contact lens. Shouldn't you make it the primary lens in your practice, too?

1. Data on file. American Optical Corp., Soft Contact Lens Div., Southbridge, MA 01550

See next page for prescribing information.

AOSOFT®
(tetrafilcon A)
HYDROPHILIC CONTACT LENSES

American Optical Corp.
SOFT CONTACT LENS DIV.
Southbridge, MA 01550

• AOSOFT® (tetrafilcon A) Hydrophilic Contact Lenses

DESCRIPTION

AOSOFT® (tetrafilcon A) Hydrophilic Contact Lens is a hemispherical shell which covers the cornea and may cover a portion of the adjacent sclera. The lens material, tetrafilcon A, is a hydrophilic random terpolymer of 2-hydroxyethyl methacrylate, N-vinyl-2-pyrrolidone and methylmethacrylate. The polymer is a three-dimensional network of terpolymer chains joined by divinylbenzene cross-links. It consists of 57.5% tetrafilcon A and 42.5% water by weight when fully hydrated in 0.9% sodium chloride solution buffered with monobasic and dibasic sodium phosphates.

ACTIONS

In its hydrated state, the AOSOFT® Hydrophilic Contact Lens is soft and pliable. When dry, the lens becomes hard and brittle. These states are completely reversible and a lens which has been permitted to dry out will recover all of its hydrated properties when placed in normal saline for a period of two hours. When placed on the human cornea, the hydrated lens acts as a refracting medium to compensate spherical ametropias. The material has a refractive index of 1.43 and the lens has a visible light transmittance greater than 97%.

INDICATIONS

AOSOFT® Hydrophilic Contact Lenses are indicated for the correction of vision in persons with non-diseased eyes who have spherical ametropias, corneal astigmatism of 2.50 diopters or less and/or refractive astigmatism of 2.00 diopters or less.

CONTRAINDICATIONS

AOSOFT® Hydrophilic Contact Lenses are contraindicated in the presence of any of the following conditions: (1) Acute and subacute inflammation of the anterior segment of the eye. (2) Any eye disease which affects the cornea and conjunctiva. (3) Insufficiency of lacrimal secretion. (4) Corneal hypoesthesia. (5) Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses.

WARNINGS

Medications and Eye Drops: AOSOFT® Lenses must be stored in an appropriate solution when off the eyes, the type of solution being dependent on the system used for disinfection. When the lenses are disinfected with the thermal disinfection system, they may be stored *only* in LENSRINS® or BOIL n SOAK® Solution (sterile, buffered preserved saline solution). When lenses are disinfected with the chemical disinfection system, they may be stored *only* in FLEXSOL® Solution (sterile, isotonic buffered solution containing Adsorbobase—a water soluble polymeric vehicle—and preserved with thimerosal 0.001%, chlorhexidine 0.005% and edetate disodium 0.1%).

No ophthalmic solutions or medications, including hard contact lens solution, can be used by AOSOFT® Lens wearers prior to or while the lenses are in place on the eyes. Also, no solutions, including hard contact lens solutions, other than LENSRINS® or BOIL n SOAK® Solution or FLEXSOL® Solution may be used on AOSOFT® Lenses when they are off the eyes.

Since liquids and vapors may be absorbed by AOSOFT® Lenses, they should not be placed in the mouth for wetting, nor wiped with a cloth or tissue.

Abrasions and Infections: If a lens becomes less comfortable than it was when first placed on the wearer's cornea, the lens should be removed immediately and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present, or any abnormal eye condition is observed concurrently with lens wear, the lens should be removed immediately and a physician consulted.

Wearing Restrictions: AOSOFT® Hydrophilic Contact Lenses should not be worn while swimming, sleeping, or in the presence of irritating fumes or vapors.

Visual Blurring: If visual blurring occurs, the lens must be removed until the condition subsides.

Lens Sanitation: Patients must adhere to the recommended daily sanitary care procedures for AOSOFT® Hydrophilic Contact Lenses. Failure to follow this procedure may result in the development of serious ocular infections.

PRECAUTIONS

Storage: AOSOFT® Lenses may be stored *only* in the appropriate storage solution: LENSRINS® or BOIL n SOAK® Solution or FLEXSOL® Solution depending on disinfecting methods used. If left exposed to air, the lenses will dehydrate, become brittle and break readily. If a lens dehydrates, it should be soaked in either LENSRINS®, BOIL n SOAK® or FLEXSOL® Solution until it returns to a soft, supple state.

Cleaning and Disinfecting: AOSOFT® Lenses must be both cleaned and disinfected daily. Separate procedures and products are needed to clean and to disinfect. Two methods of disinfection, thermal or chemical, have been shown to be equally effective. The choice of disinfection system should be made in consultation with your eye care practitioner.

Cleaning: Daily cleaning is necessary to remove mucus and other deposits which may have accumulated on the lens surface. Each time the lenses are removed from the wearer's eyes, both surfaces of the lenses must be cleaned using several drops of PREFLEX® Cleaning Solution (sterile solution of a nonionic cleaner preserved with thimerosal 0.002% and edetate disodium 0.1%). Lenses must be cleaned before they are disinfected, as deposits on the lenses tend to harden and become more difficult to remove after the lenses are disinfected.

Disinfecting: AOSOFT® Lenses may be disinfected with either a thermal or chemical regimen. One method or the other must be selected, but not both. THE USER MUST NOT ALTERNATE BETWEEN METHODS.

Thermal Disinfection Method: AOSOFT® Lenses may be effectively disinfected after cleaning with PREFLEX® Cleaning Solution with use of the AOTHERM™ Heating Unit For Lens Disinfection and LENSRINS® or BOIL n SOAK® Solution. Fresh LENSRINS® or BOIL n SOAK® Solution must be used for daily storage of lenses or each time the lens is stored. The AOTHERM™ Heating Unit For Lens Disinfection requires distilled water. The AOSOFT® Lens Storage Containers must be emptied and filled with fresh LENSRINS® or BOIL n SOAK® Solution just prior to disinfecting the lenses.

Chemical Disinfection: Disinfection with PREFLEX® Cleaning Solution, FLEXSOL® Solution and NORMOL® Rinsing Solution (sterile isotonic saline solution preserved with thimerosal 0.001% and chlorhexidine 0.005%) has also been shown to be an effective disinfection system for daily care of AOSOFT® Lenses.

AOSOFT® Lenses must be cleaned and rinsed daily (or after wearing) with PREFLEX® Cleaning Solution and NORMOL® Rinsing Solution. The AOSOFT® Lens Storage Containers must be emptied and refilled with fresh FLEXSOL® Solution each time the lens is stored. Fresh FLEXSOL® Solution must be used daily for storage and disinfection.

WARNING: DO NOT MIX OR ALTERNATE THE DISINFECTION AND STORAGE SYSTEMS. FLEXSOL® SOLUTION SHOULD NOT BE USED WITH HEAT.

Hygiene: Before handling the lenses, hands must be washed, rinsed thoroughly and dried with a lint-free towel. Cosmetics, lotions, soaps, oil and hand creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the spray has settled.

Fluorescein: Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with LENSRINS® or BOIL n SOAK® and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein.

ADVERSE REACTIONS

Serious corneal damage may result from wearing lenses which may have soaked in hard contact lens solutions. Eye irritation may occur within a short time after putting on a hypotonic lens. Removal of the lens will relieve the irritation.

Very rarely a lens may adhere to an eye as a result of a patient sleeping with the lens on, or as a result of wearing a hypotonic lens. If a lens adheres for any reason, the patient may be instructed to apply a few drops of LENSRINS® or BOIL n SOAK® Solution (if using a thermal disinfection regimen) or ADAPETTES® Cleaning and Rewetting Solution (sterile, isotonic, buffered solution containing Adsorbobase and preserved with thimerosal 0.002% and edetate disodium 0.05%) (if using a chemical disinfection regimen), and wait until the lens moves freely before removing it.

Clinical studies indicate that corneal edema as manifested by symptoms such as rainbows or halos around light or visual blurring may occur if lenses are worn continuously for too long a time. Removal of the lenses and a rest period of at least one hour generally relieve these symptoms. If symptoms do not subside promptly, professional consultation should be obtained.

Excessive tearing, unusual eye secretions and photophobia are not normal; if these symptoms occur, the patient should be examined to determine their cause.

DOSAGE AND ADMINISTRATION

Fitting: Conventional methods of fitting contact lenses do not apply to AOSOFT® (tetrafilcon A) Hydrophilic Contact Lenses. For a detailed description of the fitting technique, refer to the Fitting Guide for AOSOFT® Hydrophilic Contact Lenses, copies of which are available from: American Optical Corp., Soft Contact Lens Div., Southbridge, MA 01550.

Wearing Schedule: There may be a tendency for the patient to overwear the lenses initially. Therefore, the importance of adhering to the following initial daily wearing schedule should be stressed to the patient.

Day	Wear Time *(hours)*	Rest Period *(hours)*	Wear Time *(hours)*
1	4	2	4
2	4	2	4
3	5	2	5
4	6	2	5
5	7	2	5
6	7	1	6
7	8	1	7
8	8	1	8
9	9	1	8
10-14	10	1	balance of
15	all waking hours		waking hours*

*lenses should never be worn 24 hours a day

Lens Care and Handling: Care must be taken on the initial visit to assure that the patient is supplied with an AOSOFT® Wearer's Kit and fully understands all care and handling instructions for the lenses. As with any contact lens, regular recall visits are necessary to assure patient health and compliance with instructions.

How Supplied: Each lens is supplied sterile in a glass vial containing 0.9% sodium chloride solution buffered with monobasic and dibasic sodium phosphates. The glass vial is marked with the Vault Number, Dioptric Power, and Lot Number.

The AOSOFT® Wearer's Kit is required for lens cleaning, disinfection and storing of the lenses. The Kit may consist of either of the following:

Thermal Disinfection Regimen: AOSOFT® Wearer's Kit, AOTHERM™ Heating Unit For Lens Disinfection, LENSRINS® Solution, PREFLEX® Cleaning Solution, AOSOFT® Wearer's "How To" Book, AOSOFT® Lens Storage Container.

Chemical Disinfection Regimen: AOSOFT® Wearer's Kit, AOSOFT® Lens Storage Container, PREFLEX® Cleaning Solution, NORMOL® Rinsing Solution, FLEXSOL® Storage and Disinfection Solution, AOSOFT® Wearer's "How To" Book.

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SOFT CONTACT LENS DIV.
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"Nervous" is a label people gave her. The Eye Computer knows better.



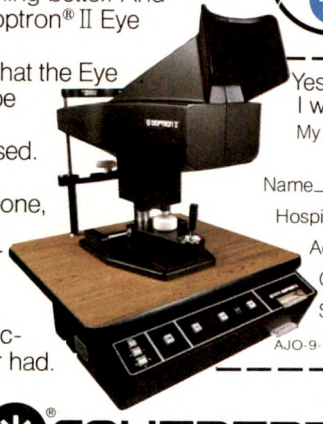
A lot of elderly patients find eye examinations totally unnerving. And many find themselves unable to concentrate for more than a few minutes at a time because of it.

While sympathy and patience will suffice for some, at least one brave lady we know decided she deserved something better. And she got it. By asking for the Dioptron® II Eye Computer directly.

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The Iris Clip Four Loop Lens by Iolab Corporation

The four loop, iris plane lens has seen a multitude of changes in its lifetime.

Some of these changes have come about through the close cooperation of Iolab and members of the implant community. The cooperation is shown in our product.

- ☐ Well defined loop angle geometry
- ☐ Easily discernable dioptic power
- ☐ Rigidly controlled clearance between the posterior surface of the lens and the posterior loop for proper iris clearnace
- ☐ First to introduce weight saving, non-biodegradable, polypropylene loop construction

By choosing this lens design for implantation you've aligned yourself with an exceptional group of implanting surgeons. We feel we make a lens worthy of this group.

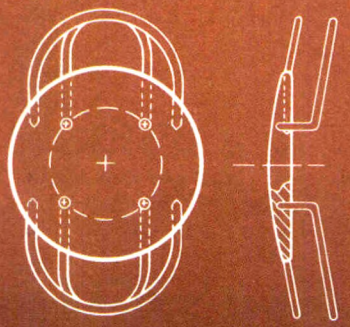
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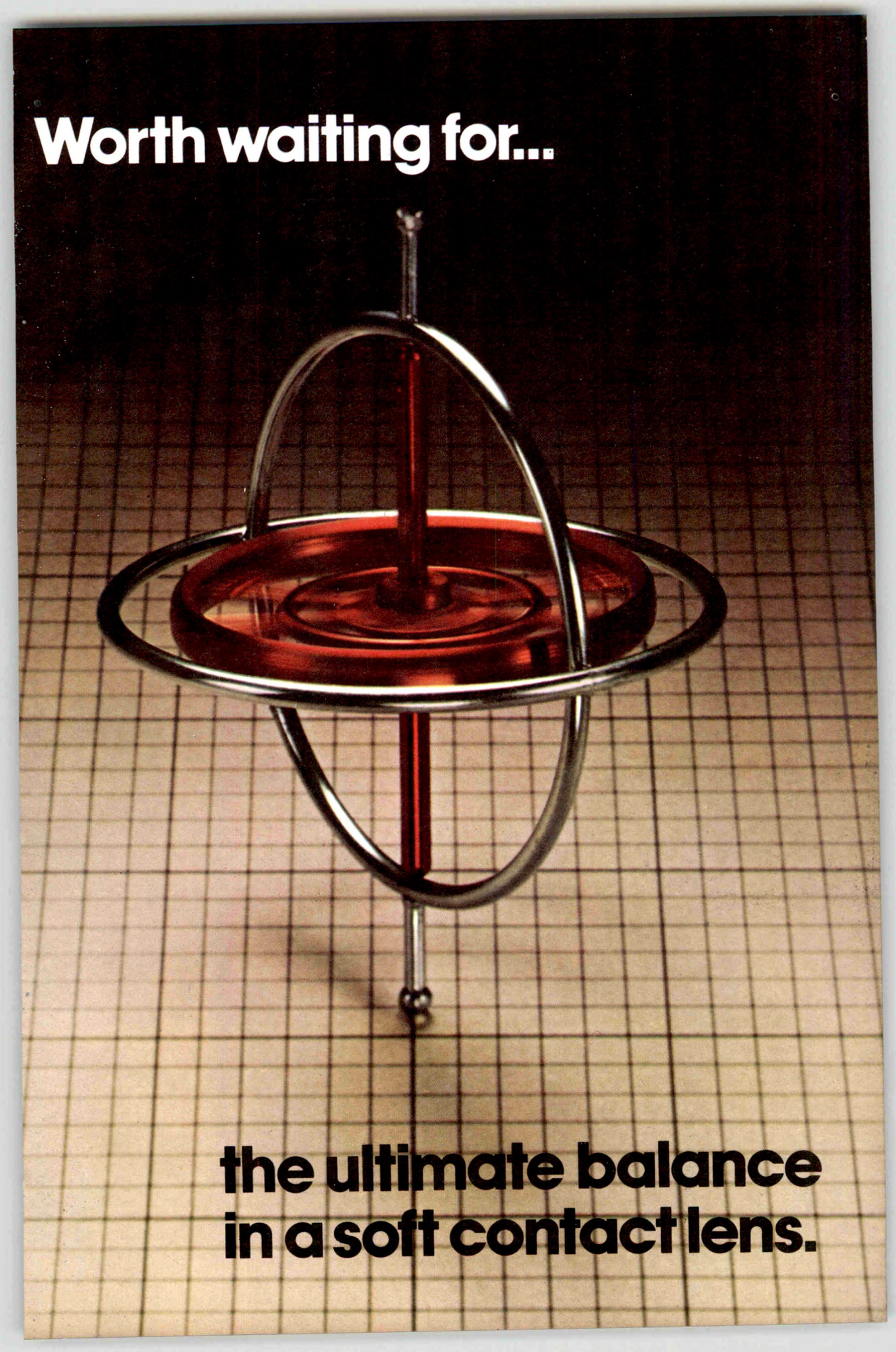
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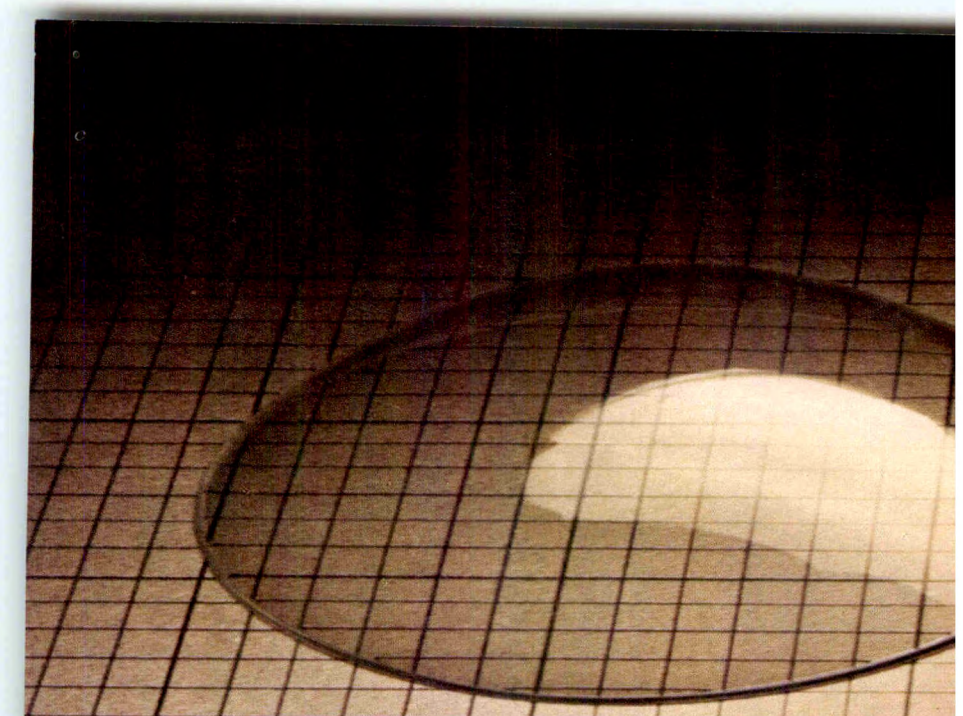


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Worth waiting for...



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Announcing...

Softcon® (vifilcon A) CONTACT LENS FOR VISION CORRECTI

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Balance—the key to Softcon performan

Meets the needs of patient and practitioner.
Suits the needs of the daily, as well as occasiona

- No adaptation period is necessary.
- Immediate comfort, first day...all day...ev
- Visual acuity of 20/20 or better, in 97% of p
- Utilizes the convenient "cold" disinfectior
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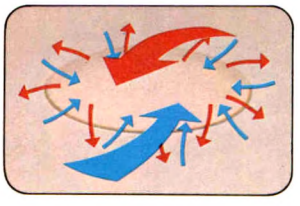
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Balance—the key to Softcon comfort

Lens water content of 55%.
Hydroequivalence closest to that of cornea.

- Enhances lens/cornea compatibility.
- Ensures wearer comfort without compromising handling or optical properties.
- Improves permeability and fluid exchanges.
- Maintains constant environment of fresh tears due to exceptional tear pump action.





Balance—the key to Softcon fit

Computerized lens geometries.
Lathe-cut miniscleral configuration.

- Provides uniform carrier geometry for all lens powers.
- Offers "fast-fit" techniques in 6 lens geometries (3 of which will fit 80% of patients).
- Achieves superior centration and stable visual acuity.
- Permits refined power adjustment without compromising fit and comfort.



Softcon® (vifilcon A) meets the toughest tests with the softest touch

American Optical Corp.,
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Southbridge, MA 01550

See next page for full prescribing information. For further details, fill out and mail this coupon.

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☐ Send information.

☐ Have representative call on _____
(Best Day) (Best Time)

The SOFTCON Lens was worth waiting for.

☐ Here is my order for SOFTCON Lenses.

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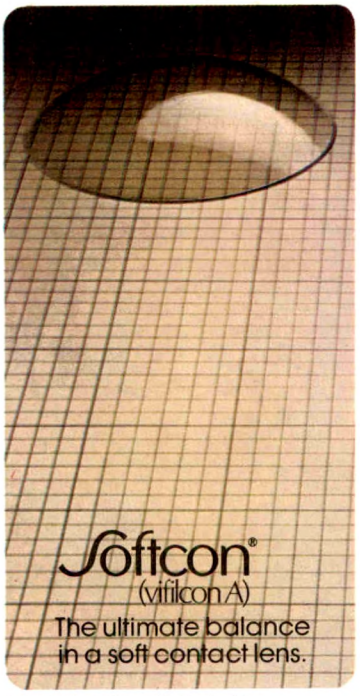
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AJO



SOFTCON® (vifilcon A) Contact Lens
Vision Correction Use

DESCRIPTION The SOFTCON (vifilcon A) Contact Lens is a hemispherical flexible transparent shell which covers the cornea and part of the sclera. The lens is composed of vifilcon A, a soft hydrophilic plastic co-polymer of 2-hydroxyethyl methacrylate and povidone, USP. The chemical name is: Poly (2-hydroxyethyl methacrylate-co-ethylene dimethacrylate-co-methacrylic acid-g-povidone). When fully hydrated, the lens contains about 55% water by weight.

INDICATIONS The SOFTCON Contact Lens is indicated for the correction of visual acuity in persons with non-diseased eyes and in aphakia. It is indicated for persons who have spherical ametropias, refractive astigmatism usually 1.50 diopters or less and/or corneal astigmatism of 2.00 diopters or less.

CONTRAINDICATIONS Presence of any active infection or inflammation of the eye, insufficient tears, corneal hypoesthesia or any systemic disease which may affect the eye adversely or be exaggerated by wearing contact lenses.

WARNINGS Medications and Eye Drops—The SOFTCON Contact Lens must be stored only in FLEXSOL® soaking solution. **NEVER USE CONVENTIONAL HARD CONTACT LENS PRODUCTS WITH THE SOFTCON CONTACT LENS.** No ophthalmic solutions or medications may be used by SOFTCON Contact Lens wearers immediately prior to or during wear of the lens. No solutions other than PREFLEX®, FLEXSOL, and NORMOL® used for cleaning and chemical disinfection may be used.

Aphakic Patients—Patients who have undergone surgery for cataract removal should not be fitted with SOFTCON Contact Lenses during the immediate post-operative period, until, in the opinion of the surgeon, the eye has healed completely.

Abrasions and Infections—If a lens becomes less comfortable to the wearer than when it was first placed on the cornea, the lens should be removed immediately, and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present, or any abnormal eye condition is observed concurrently with lens wear, the lens should be removed immediately and a clinician must be consulted.

Lens Care—WEARERS MUST ADHERE TO THE RECOMMENDED DAILY CLEANING, CARE AND DISINFECTION REGIMEN AS DESCRIBED IN THE SOFTCON WEARER'S BOOKLET. FAILURE TO ADHERE TO THE RECOMMENDED PROCEDURES MAY RESULT IN THE DEVELOPMENT OF SERIOUS EYE INFECTION.

Wearing Restriction—The lens should be removed before sleeping or swimming, and should not be worn in the presence of irritating fumes or vapors.

Visual Blurring—If unusual visual blurring occurs, the lenses must be removed until the condition subsides. If blurring persists see your eye care practitioner.

PRECAUTIONS Storage—The SOFTCON Contact Lenses must be stored only in FLEXSOL soaking solution. If left exposed to air, the lenses will dehydrate, becoming hard and easily damaged. If a lens dehydrates, it should be carefully handled and soaked again in FLEXSOL until it returns to its normal soft, supple state.

Cleaning and Disinfection—THE SOFTCON CONTACT LENS MUST BE BOTH CLEANED AND DISINFECTED DAILY. ONE PROCEDURE DOES NOT REPLACE THE OTHER.

Cleaning—Daily cleaning is necessary to remove mucus and other deposits which may have accumulated on the lens surface from normal ocular secretions, airborne debris, or handling. The lenses must be cleaned before being disinfected, as deposits on the lens tend to harden and become more difficult to remove after the lenses are disinfected.

Disinfection—Lenses must be disinfected daily according to the chemical disinfection regimen. For chemical disinfection, all three solutions, PREFLEX, FLEXSOL, and NORMOL, must be used and must be changed daily. In the event that the chemical disinfection materials are not available, the lenses should not be worn.

Hygiene—Hands must be washed, rinsed thoroughly and dried with a lint-free towel before handling the lenses. COSMETICS, lotions, soaps, oils and hand creams must not come in contact with the lenses since eye irritation may result. If aerosol sprays are used while the lenses are being worn, the eyes must be kept tightly closed until the sprays have settled.

Fluorescein—Use of fluorescein while the patient is wearing the lenses may cause the lenses to become discolored. Whenever fluorescein is used, irrigate the eyes with preserved normal saline solution, and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein irreversibly.

ADVERSE REACTIONS Serious corneal damage may result from wearing lenses which have been soaked in conventional (hard) contact lens solutions.

Eye irritation may occur within a short time after applying a hypertonic lens. Removal of the lens will relieve the irritation. Very rarely, a lens may adhere to an eye as a result of a patient sleeping with the lens on or while wearing a hypotonic lens. If a lens adheres for any reason, apply a few drops of ADAPETTES® directly to the eye and wait until the lens moves freely before removing it.

Clinical studies indicate that corneal edema as manifested by symptoms such as rainbows or halos around lights, or visual blurring may occur if lenses are worn for too long a time. Removal of the lenses and a rest period of at least one hour generally relieves these symptoms. If symptoms do not subside promptly, or if excess tearing, unusual secretions, or photophobia develop, professional consultation should be obtained.

DOSAGE AND ADMINISTRATION Fitting—Usual methods of fitting conventional (hard) contact lenses do not apply to the SOFTCON Contact Lens.

For a detailed description of the fitting technique, refer to the SOFTCON Fitting Booklet.

Wearing Schedule—The wearing schedule should be determined by the eye care practitioner. Studies have not been performed to support the safety of this lens for longer than the recommended wearing time.

Patients should wear their lenses for 8-16 hours on the day the lenses are dispensed. If patients cannot tolerate 16 hours of lens wear daily, the eyes should be examined and the lens fit re-evaluated.

Lens Care and Handling—Care must be taken on the initial visit to assure that the patient is supplied with a SOFTCON Care Kit and fully understands all proper care and handling procedures for the lenses. As with any contact lens patient, regular re-examination visits are necessary to assure ocular health and patient compliance with instructions.

How Supplied—Each lens is shipped sterile in a sealed glass vial containing buffered normal saline solution. The vial label is marked with the base curve, dioptric power, diameter and the manufacturing identification number of the lens.

Patient Care Kit—The SOFTCON Care Kit is a package required for cleaning, disinfection and storage of the lenses. It consists of the following:

- Carrying & Storage Lens Case
- PREFLEX® Sterile Cleaning Solution
- FLEXSOL® Sterile Disinfection and Storage Solution
- NORMOL® Sterile Rinsing Solution
- ADAPETTES® Sterile Lubricating Solution
- SOFTCON Wearer's Booklet

Caution: Federal law prohibits dispensing without prescription.

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Printed in U.S.A. Aug. 1978 60024

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When you want a sharper, brighter image of the eye fundus, look to Nikon. Nikon introduces its new multi-layer-coated aspherical lenses that reduce nearly all harmful light reflection while transmitting more visible light, to give you the sharpest, clearest image of the eye fundus you have ever seen.

These new Nikon Clear Coat aspheric lenses eliminate spherical aberration and coma. Peripheral blur is overcome, so that the image is clear and accurate.

In addition to the sharp, minimally distorted image, you get uniform brightness, larger apertures, and light weight.

New Nikon Clear Coat aspherical lenses are available in 14, 20, and 28 diopters. For complete information, write or call Nikon Inc., Instrument Division, Ophthalmic Department, Ehrenreich Photo-Optical Industries, Inc., 623 Stewart Ave., Garden City, N.Y. 11530; (516) 222-0200. **Look to *Nikon***

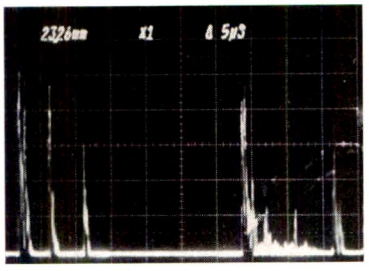


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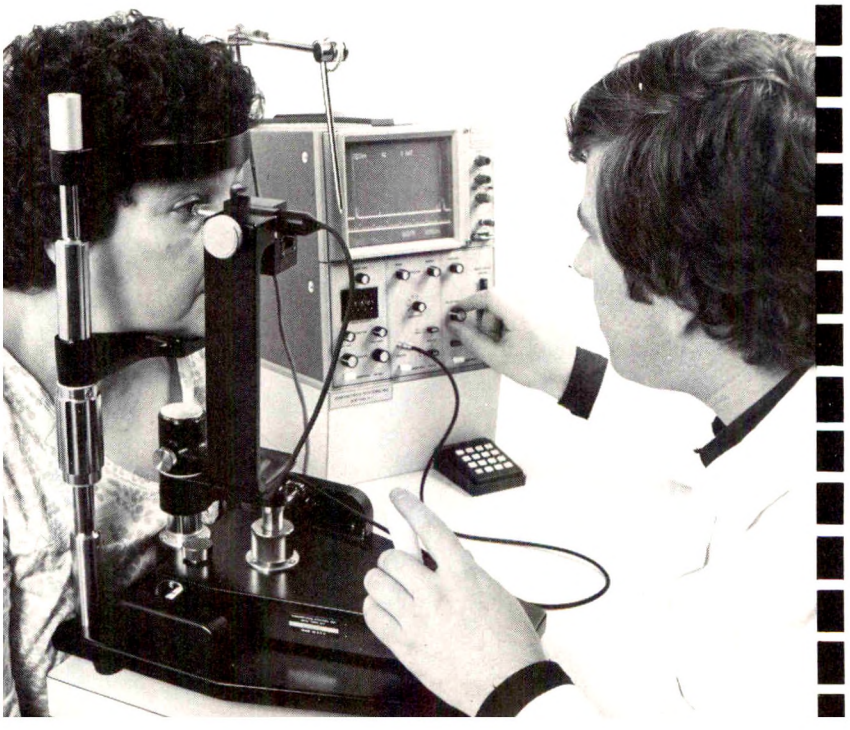
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DBR-300 oscilloscope presentation showing characteristic A-scan pattern along the visual axis and simultaneous readout of axial length in millimeters.



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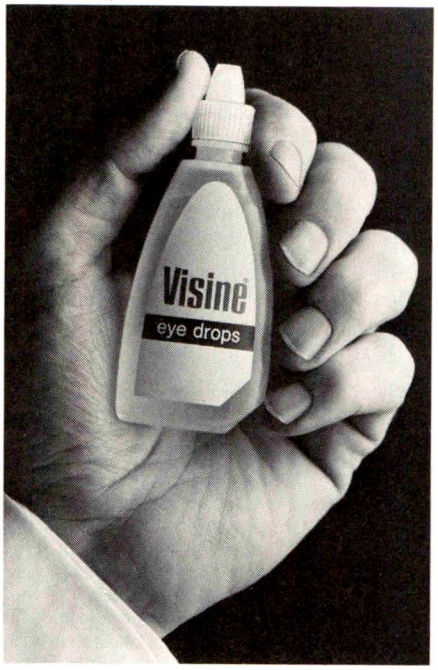
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Extensive clinical tests* indicate Visine is ideally suited for your recommendation.



Visine® has been proven safe and effective for relief of symptoms of minor eye irritation.

Whatever causes your patients' minor eye irritation—glare, pollen, close work or air pollution—Visine provides fast relief. It relieves the burning and itching, and its vasoconstrictor (tetrahydrozoline HCL) effectively removes redness from the eye.

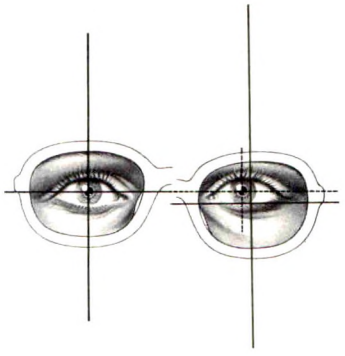
For this relief, more people already use Visine than any other eye drop. And this widespread acceptance plus Visine's extensive clinical testing means you can recommend Visine to your patients with confidence.

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Visine Eye Drops is another quality product from Pfizer Inc.

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Unlike ordinary plastic eyeglass frames, OPTYL frames maintain their adjusted optical center, do not distort or require constant re-alignment.



The secret of OPTYL's stability is in its molecular filaments and their chemical bonding. Ordinary acetate or celluloid frames have filaments that are not uniformly distributed throughout the frame material. The filaments are physically mixed and interspersed in irregular patterns, leading eventually to structural weakness. Plasticizers, added to strengthen the material, are likewise scattered and irregularly distributed among the filaments. Both the filaments and plasticizers move or "creep" within the material, affecting frame fit and requiring repeated adjustments by the optical dispenser.

OPTYL® frames maintain their fit and comfort regardless of anatomical variations of the human head.



Unfortunately, the human head does not provide an ideal standard support for eyeglasses. Noses, bridges, and ears differ. It rarely occurs that the head is perfectly bisymmetric. Yet for frames to fulfill their function in holding corrective lenses in front of the eyes, they must fit firmly on the head. To keep eyeglasses accurately positioned, supporting points, such as the bridge and ears, and friction are necessary. This means that frames are subject to continuous tension when worn.

Because the "creep" or movement of filaments in acetate frames is accentuated by this tension, a proper fit cannot be maintained over a prolonged period. When frame distortion occurs, pressure on supporting points may become excessive, leading to pressure necrosis, damage to underlying tissue and discomfort.

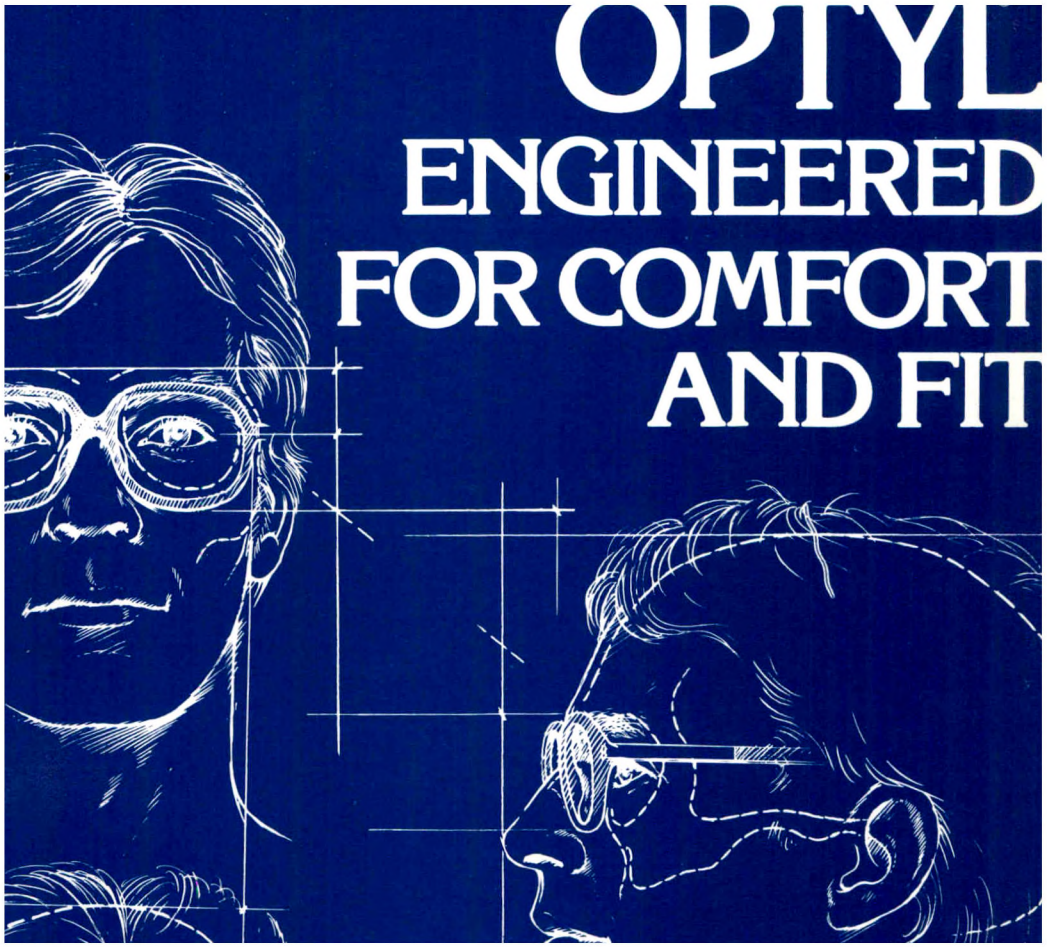
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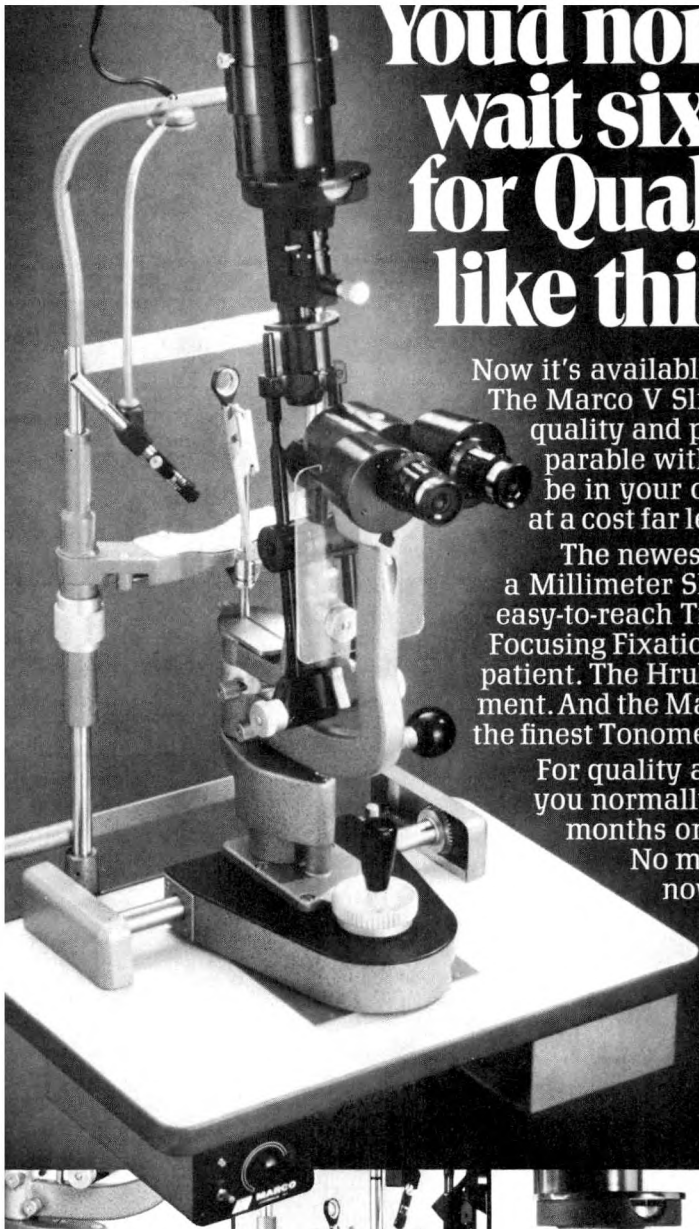


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You'd normally wait six months for Quality like this...

Now it's available immediately. The Marco V Slit Lamp, with optical quality and precision controls comparable with any to be found, can be in your office tomorrow . . . and at a cost far less than you might expect.

The newest model Marco V features a Millimeter Slit Length Control, an easy-to-reach Tilting Mechanism and a Focusing Fixation Light adjustable to each patient. The Hruby lens is standard equipment. And the Marco V is designed to accept the finest Tonometers and Pachometers.

For quality and flexibility like this, you normally could expect to wait six months or longer for delivery.

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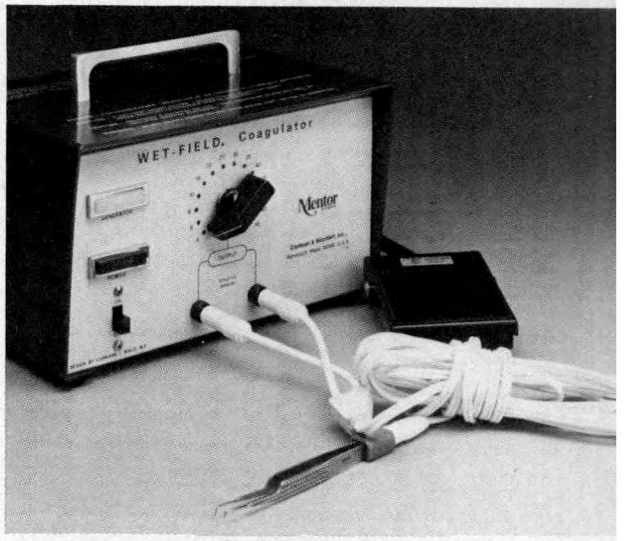
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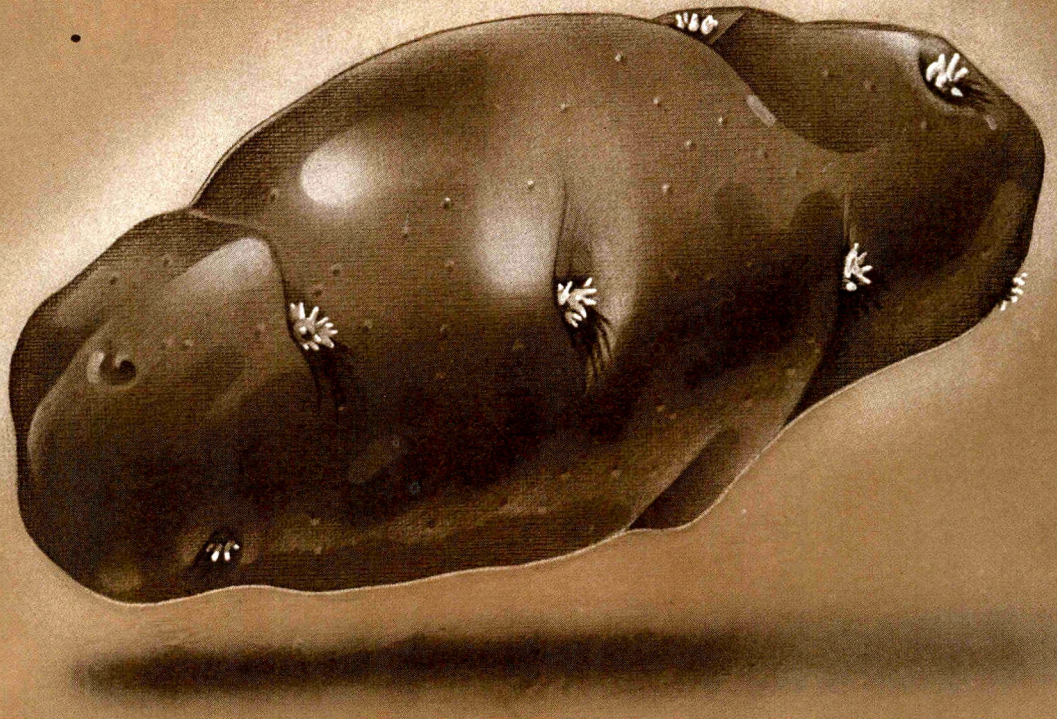
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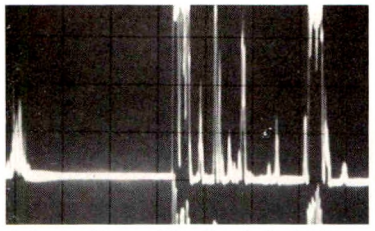
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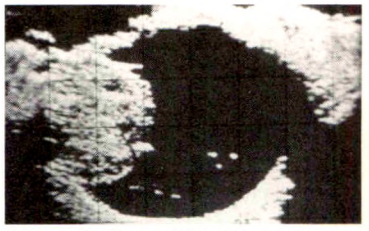
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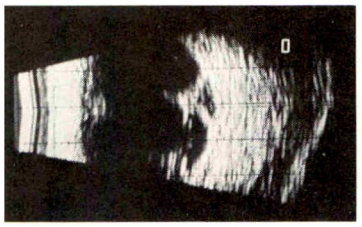
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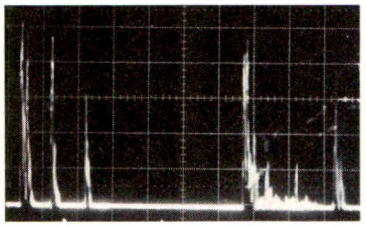
1. *A-scan* of tumor of the ciliary body showing attenuation pattern of a malignant melanoma.



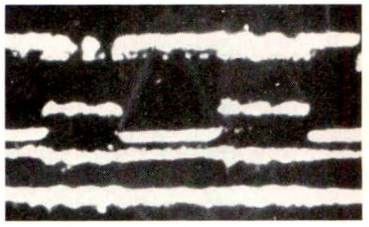
2. Immersion *B-scan* of the same melanoma with posterior vitreous hemorrhage.



3. Contact *B-scan* through a closed lid shows distinctive "X" shape of vitreous membranes and traction retinal detachment in diabetic retinopathy.

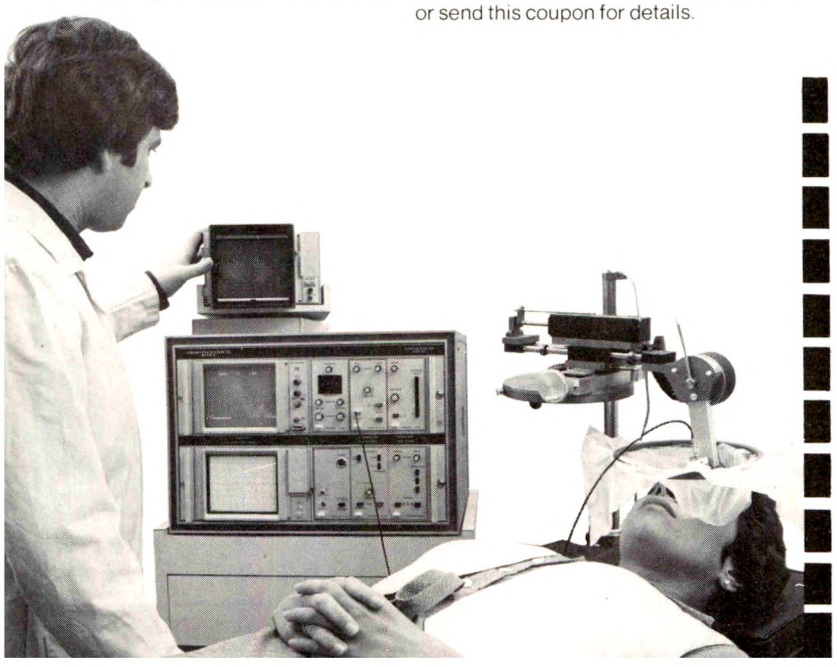


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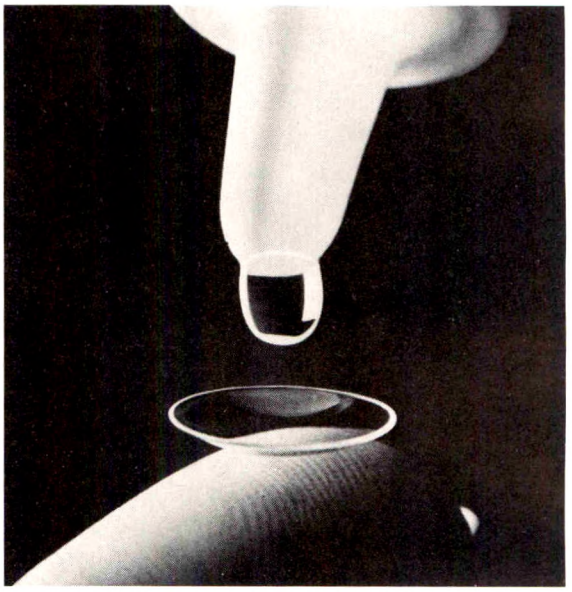
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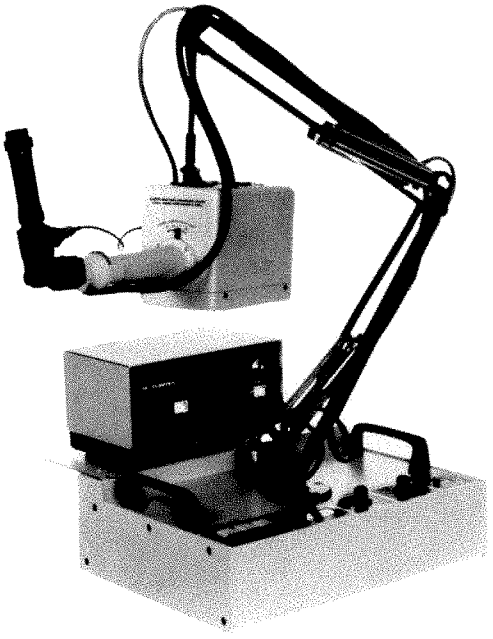
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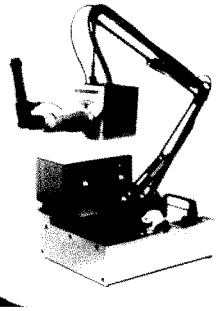
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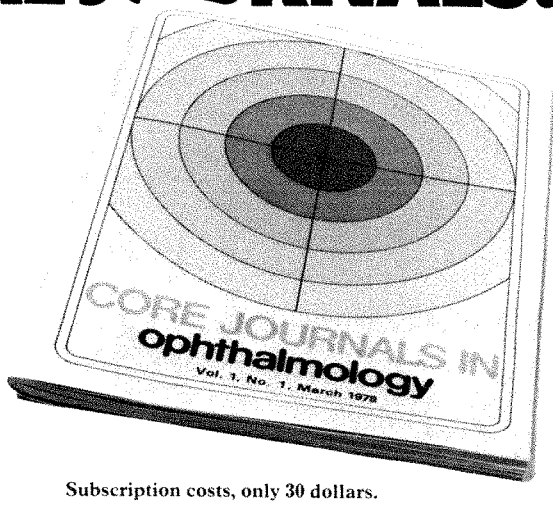
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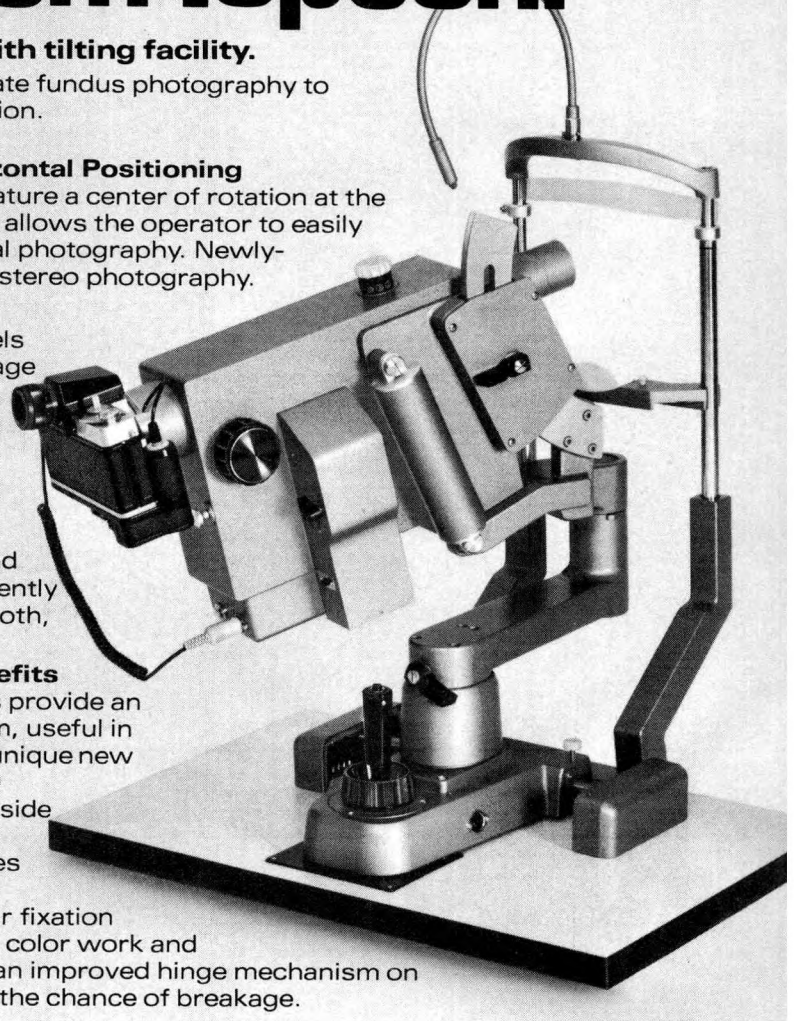
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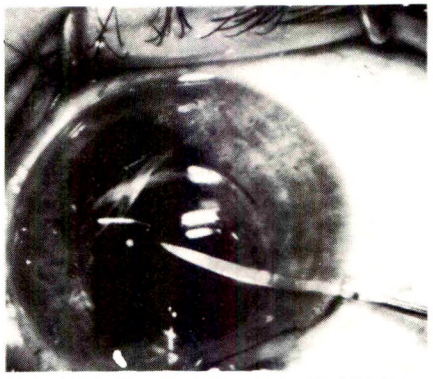
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Marvin L. Kwitko, M.D., Attending Ophthalmologist St. Mary's Hospital and Sir Mortimer Davis Hospital, Project Director in Ophthalmology, Lady Davis Institute for Medical Research, Canada



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ANNOUNCES

A

VITRECTOMY WORKSHOP

Emphasizing bimanual techniques with the OCUTOME/FRAGMATOME SYSTEM in surgery of the anterior and posterior segments.

FRIDAY AND SATURDAY
November 3, 4, 1978

To be held at:
MASSACHUSETTS EYE AND EAR INFIRMARY
243 Charles Street
Boston, Massachusetts 02114

GUEST FACULTY

Thomas M. Aaberg, M.D.
Steve Charles, M.D.
D. Jackson Coleman, M.D.
Maurice B. Landers, III, M.D.
George O. Waring, M.D.

Albert R. Frederick, Jr., M.D. Course Director
Michael J. Bradbury, M.D. Course Coordinator

OBJECTIVES:

The two-day workshop will cover pars plana vitrectomy and anterior segment techniques using bimanual microsurgical vitrectomy instrumentation.

PROGRAM:

Morning didactic sessions will cover basic concepts, surgical indications, diagnostic methods and surgical techniques.

Afternoon sessions will consist of practice surgery on animal eyes using the Ocutome/Fragmatome instruments supervised directly by the faculty. Anterior or posterior segment techniques will be emphasized depending on your interest and needs.

Registration Fee:
$400.00 complete workshop
$100.00 morning sessions only
ENROLLMENT LIMITED

For Registration Information:
Albert R. Frederick, Jr., M.D.
Course Director
50 Staniford Street
Boston, Massachusetts 02114

NEURO-OPHTHALMOLOGY

clinical signs and symptoms

By THOMAS J. WALSH, M.D., *Yale University, School of Medicine, New Haven, Connecticut. With chapters by* STEPHEN L.G. ROTHMAN, M.D., ROBERT B. WELCH, M.D., *and* PETER D. WILLIAMSON, M.D. Directed to both practicing and resident ophthalmologists, this clinically useful book focuses on the practical application of well-accepted diagnostic tests and techniques and the interpretation of information for sound differential diagnosis. The specialist can use this text as an office reference in that each of the 13 chapters is devoted totally to one condition. Each chapter has been written in the form of a monograph. Since the book is intended for use in a clinical situation, the physician's familiarity within the discipline of ophthalmology has been assumed. Avoiding rare and unusual disorders unless critical to the patient's vision or general health, the book provides a unique symptom and sign format for diagnosing such problems as pupillary abnormalities, decreased vision, or nystagmus. Thus each chapter deals with either a symptom that leads the patient to seek medical attention or a sign that is demonstrated on physical examination. The physician can then turn to that chapter and have the pertinent clinical data needed for examination of the patient and for evaluating the most common diseases. For those who seek additional clinical evidence, and those who want to further explore a given subject in the literature, pertinent bibliographic references are liberally supplied. *294 pp. (7 x 10), illus. (some in color), 1978, $22.50.*

2 other titles

A New Book! **ULTRASONOGRAPHY OF THE EYE AND ORBIT.** *By* D. JACKSON COLEMAN, M.D., *Columbia University, College of Physicians and Surgeons, New York, New York;* FREDERIC L. LIZZI, Eng.Sc.D., *Riverside Research Institute, New York, New York; and* ROBERT L. JACK, M.D., Med.Sc.D., *Stanford University School of Medicine, Palo Alto, California.* "The most comprehensive book on the subject in the current literature...an authoritative textbook on ocular B-scan ultrasonography."—*Mayo Clinic Proceedings. 376 pp. (7 x 10), illus. (2 in color), 1977, $35.00.*

A New Book! **GLAUCOMA GUIDEBOOK.** *By the late* GERALD L. PORTNEY, M.D. This practical and clearly written book will serve as an introduction to glaucoma, as well as a ready reference to the many clinically relevant aspects of this disease. The text deals with everyday judgements for the management of glaucoma and gives explicit directions on how to perform the essential diagnostic tests which form the basis for these clinical decisions. Its coverage of projection perimetry and slit lamp evaluation of the optic disc is unique to the literature. *158 pp. (5¼ x 7¾), illus.*, 1977, $9.75.

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March 8, 9, 10, 1979

Anatole Hotel • Dallas, Texas

PURPOSE

The multitude of new ophthalmological diagnostic tests now available is a source of great confusion to many practitioners. The goal of this program is to present a meeting which will explain these tests as simply as possible and suggest a logical approach to their utilization.

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Eliot Berson, M.D., Boston
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Peter Bringewald, M.D., Dallas
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Featured speakers include Drs. Crowell Beard, Alston Callahan and Byron Smith. Special guest lecturer will be Leo Koornneef, Department of Anatomy and Embryology, University of Amsterdam, Holland.

Registration fee before September 30th is $60.00, after that date $75.00. Residents and paramedical $30.00 before September 30th with letter from personnel department chairman, after 30th $40.00

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Department of Ophthalmology, University of Minnesota

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CONTRAINDICATIONS: These products are contraindicated in acute purulent conjunctivitis and blepharitis; tuberculous, fungal or viral lesions of the skin or eye, including herpes simplex, dendritic keratitis, vaccinia or varicella; and conditions involving the posterior segment of the eye. They are also contraindicated in those individuals who have shown hypersensitivity to any of their components.

PRECAUTIONS: Extended ophthalmic use of topical steroid therapy may result in glaucoma with possible damage of the optic nerves, posterior subcapsular cataract formation, or may aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissues. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids. As with any antibiotic preparation, prolonged use may result in the overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

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St. Vincent's Hospital and Medical Center of New York

ANNUAL CLINICAL UPDATE

Eastern Regional Meeting – Contact Lens Association of Ophthalmologists, Inc.

Wednesday, Thursday & Friday *November 1, 2, & 3, 1978*

Robert A. D'Amico, M.D.
Director, Department of Ophthalmology

G. Peter Halberg, M.D.
Meeting Coordinator

COMPLICATIONS OF CATARACT AND OTHER INTRAOCULAR SURGERY

Wednesday, November 1

GLAUCOMA • CONTACT LENS

G. Peter Halberg, M.D., Chairman

Thursday, November 2

CORNEA

Robert A. D'Amico, M.D., Chairman

INTRAOCULAR LENS

Richard D. Binkhorst, M.D., Chairman

Friday, November 3

RETINA • VITRECTOMY

Ruth Stoddard Long, M.D., Chairman

FACULTY

Joseph A. Baldone, M.D.
Richard D. Binkhorst, M.D.
Jorge N. Buxton, M.D.
Mary Bruch
Delmar R. Caldwell, M.D.
Dean Clements
Oliver H. Dabezies, Jr., M.D.
Robert A. D'Amico, M.D.
C. Richard Elander, M.D.
R. Linsy Farris, M.D.
Gerald L. Feldman, Ph.D.
John R. Finlay, M.D.
William S. Hagler, M.D.
G. Peter Halberg, M.D.
Jack Hartstein, M.D.
Jonathan Herschler, M.D.
Paul R. Honan, M.D.
Ronald P. Jensen, M.D.
Herbert E. Kaufman, M.D.
James J. Koverman
Harvey A. Lincoff, M.D.
Donald L. MacKeen, Ph.D.
Francis Manapoli, M.D.
Leroy G. Meshel, M.D.
Murray Sibley, Ph.D.
Ruth Stoddard Long, M.D.
H. Roth, M.D.
Morton L. Rosenthal, M.D.
Max Talbott, Ph.D.
William M. Townsend, M.D.
Richard C. Troutman, M.D.
Thom Zimmerman, M.D.

REGISTRATION (Clinical Update): **$240.00 (includes luncheon and a social function)**
$140.00 for Residents

Saturday, November 4

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This *intensive,* practical "Hands On" course will be under the direction of G. Peter Halberg, M.D., with the cooperation of the distinguished faculty and the major soft contact lens manufacturers.

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CONTRAINDICATIONS:
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WARNINGS:
Prolonged use may result in overgrowth of nonsusceptible organisms. Ophthalmic Ointment may retard corneal healing.

PRECAUTIONS:
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Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

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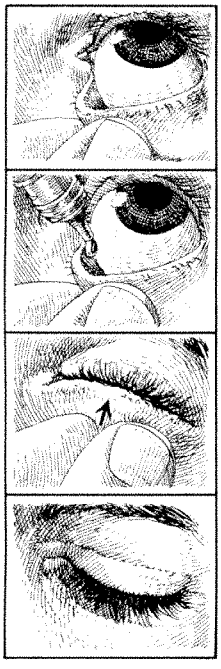
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4
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1. Fraunfelder FT, Hurwitz J, Marsey M: Presentation at Las Vegas Meeting of Association for Research in Vision and Ophthalmology and the American Academy of Ophthalmology and Otolaryngology, Oct. 6, 1976, as reported in *Clinical Trends in Ophthalmology*, April 1977.

In a controlled study comparing a variety of common techniques, retention of eye drops on the eye after a five-minute interval went from 16% to 53% when the pouch technique was utilized in the under 20 age group. A 64% retention rate was achieved in the 50-60-year-old age group.

See adjacent page for brief prescribing information.

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November 1-4, 1978

OBJECTIVES:
An in-depth symposium to provide the practicing and resident surgeon with an Oculoplastic Course featuring LIVE SURGERY VIDEO TAPES, FILMS, LECTURES AND PARTICIPANT'S CADAVER SURGERY.

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I. Baras, M. D.	P. Guibor, M. D.
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B. Cosman, M. D.	L. Herman, PhD.
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M. Guibor, C. O.	and others.

SUBJECTS:
Cosmetic Blepharoplasty, Blepharoptosis, Trauma Surgery, Lid Reconstruction, Lacrimal Surgery, Orbital Reconstruction, Entropion, Ectropion, Orbital Fractures and Orbital Tumors.

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OCULOPLASTIC COURSE

VII NERVE SURGICAL DISSECTION COURSE

(25 HRS. CME & CAT I)

October 29-31, 1978

OBJECTIVES:
A unique and practical surgical course, presented by multiple disciplines, covering the management of FACIAL PALSY and FACIAL SPASM, featuring PARTICIPANT'S CADAVER SURGERY.

FACULTY:

L. Bergmann, M. D.	M. May, M. D.
J. Conley, M. D.	S. Parisier, M. D.
M. Dunn, M. D.	H. Settles, PhD.
F. Gillen, M. D.	J. Smith, M. D.
P. Guibor, M. D.	D. Wolfley, M. D.
P. Janetta, M. D.	D. Zorub, M. D.

SUBJECTS:
Facial Nerve Testing, Dynamic-Static Techniques, Lid Spring, Silicone Encircling, Facial Reconstruction, Direct Nerve Repair and Grafting, 12-7 Hook-up Animation, Neuromuscular Pedicle Transfer and Nerve Avulsion.

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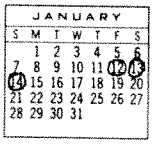
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Jorge N. Buxton, M.D.
Post Surgical Visual Rehabilitation

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Present Status of Keratophakia for the Correction of Hyperopia and Aphakia

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Mr. Jack Moore
A Practical Approach for the Average Clinical Practice

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iday, January 12

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J. Elliott Blaydes, Jr., M.D. and
Robert J. Crossen, M.D., Co-Moderators
Other Participants to be Announced

SYMPOSIUM: PROLONGED WEAR - UPDATE
Walter J. Stark, M.D., Moderator
Other Participants to be Announced

Mary Bruch
Food and Drug Administration

THIRD ANNUAL THEODORE E. OBRIG MEMORIAL LECTURE
Mr. Jack Moore
A Practical Approach for the Average Clinical Practice

SPORTS AND CONTACTS
Richard H. Keates, M.D.

DISTINGUISHED VISITING LECTURER
José I. Barraquer, M.D.
Present Status of Keratophakia for the Correction of Hyperopia and Aphakia

CONTACT LENS COURSES

(Pre-registrants may select courses by mail)

Saturday, January 13

SYMPOSIUM: ASTIGMATISM - SURGICAL CORRECTION

Herbert E. Kaufman, M.D., Moderator

Other Participants to be Announced

SYMPOSIUM: THE CONTACT LENS CORRECTION OF ASTIGNMATISM

Joseph A. Baldone, M.D., Moderator

Other Participants to be Announced

THE FUTURE WAS YESTERDAY

Lawrence A. Winograd, M.D.

ELEVENTH CONRAD BERENS LECTURE

Jorge N. Buxton, M.D.

Post Surgical Visual Rehabilitation

SYMPOSIUM: PITFALLS IN LENS IMPLANTATION

Harold A. Stein, M.D., Moderator

Errors in Patient Selection ..... Harold A. Stein, M.D.
Pitfalls at the Time of Surgery ..... Richard Kratz, M.D.
Pitfalls in the Immediate Post-op Period ..... Marvin Kwitko, M.D.
Pitfalls in the Late Post-op Period ..... Herve Byron, M.D.
Guiding the Resident in Lens Implantation ..... Leeds Katzin, M.D.

Question and Answer Period

SYMPOSIUM: SURGICAL TECHNIQUES FOR VARIOUS IMPLANTS (Movies)

Jack Hartstein, M.D., Moderator

Technique with the Copeland Lens ..... Ned Snyder, M.D.
Technique with the Copeland Lens ..... William U. McReynolds, M.D.
Medallion Lens in Association with Intracapsular Cataract Extraction ... Manus C. Kraff, M.D.
2-Loop Binkhorst Lens ..... Richard Kratz, M.D.
4-Loop Binkhorst Lens ..... Henry Hirschman, M.D.
Federov Sputnik Lens and the Platinum Clip Lens ..... Marvin L. Kwitko, M.D.
Primary Implants of the Choyce Lens ..... Jerald L. Tennant, M.D.
Secondary Implantation of the Azar Tripod ..... Robert Azar, M.D.
Shearing Lens ..... Steven P. Shearing, M.D.
Suturing Techniques ..... C. William Simcoe, M.D.

Panel Discussion

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ANALYSIS OF CORNEAL CRYSTALLINE DEPOSITS IN MULTIPLE MYELOMA

GORDON K. KLINTWORTH, M.D., STEVEN J. BREDEHOEFT, M.D., AND JOHN W. REED, M.D.

Durham, North Carolina

Two decades ago Bürki[1] described a patient with multiple myeloma and bilateral corneal crystals. Since then the presence of numerous delicate scintillating crystals within the cornea has become recognized as a rare manifestation of hypergammaglobulinemia,[2-4] and as possibly the first clinical evidence of systemic disease. In some cases the corneal crystals have appeared interspersed throughout the corneal stroma, whereas in others they were most evident in the anterior cornea.[2] Crystals may be detectable clinically in the bulbar conjunctiva,[2,4] but have not been observed in other ocular tissues in patients with hypergammaglobulinemia. Handley and Arney[5] described crystalline deposits in the cornea and lens of a patient with what they called plasma cell myeloma, but the evidence does not substantiate the diagnosis. Also, hypergammaglobulinemia was not present in their patient. Morphologic observation of the corneal crystals in hypergammaglobulinemia has heretofore only been documented by Pinkerton and Robertson[4] who identified intracellular crystals in the conjunctiva, corneal stroma, and bone marrow by electron microscopy.

We report herein a detailed analysis of the nature of the corneal crystals in a patient with multiple myeloma and the association of corneal crystals with crystalline deposits in the lens of another patient with multiple myeloma.

CASE REPORTS

Case 1—In 1961 a 46-year-old woman came here complaining of pain and swelling of the left great toe associated with multiple episodes of bone and joint pain. The patient had been in good health until 1951 when she developed low back pain with sciatica and underwent repair of a herniated disk. Despite extensive examination, no evidence could be found of gout or rheumatoid arthritis. Her serum protein at this time was 9.2 g/100 ml with an albumin fraction of 4.2 g/100 ml. A serum protein electrophoresis was not performed, but the presence of a 5 g/100 ml nonalbumin protein fraction prompted examination of the urine for the presence of Bence-Jones protein. This test was negative. In 1962 a hysterectomy was performed for uterine bleeding secondary to fibroids. When seen here in September 1962, the patient was anemic with a hemoglobin of 9.2 g/100 ml. She began to receive an experimental drug, MK-615, which was discontinued after three months because of visual impairment and the presence of numerous crystals in the cornea. Some observers thought the crystals might be related to MK-615. At that time visual acuity was 6/6 (20/20) in both eyes. In 1963 anemia and multiple joint pains were again evident. A bone marrow aspirate was unremarkable except for the absence of stainable iron, and no crystals were identified in it. X-ray examination of the left great toe showed a loss of density, but no definite changes attributable to gout

From the Departments of Pathology (Drs. Klintworth and Bredehoeft) and Ophthalmology (Drs. Klintworth and Reed), Duke University Medical Center, Durham, North Carolina. This study was presented in part at the Association for Research in Vision and Ophthalmology meeting in Gainesville, Florida, Nov. 17-19, 1977; it was supported in part by U.S. Public Health Service Grant 2 RO1 EY 00146 (Dr. Klintworth).

Reprint requests to Gordon K. Klintworth, M.D., Department of Pathology, Duke University Medical Center, Durham, NC 27710.

or rheumatoid arthritis. Joint pains and recurrent epistaxis continued for many years. A peptic ulcer with gastrointestinal bleeding was treated in 1971; in 1976 she had severe pain in the low thoracic-lumbar area and began to lose weight.

In August 1976, at age 60, the patient was admitted here because of a progressive painless diminution in vision that extended over several years. Visual acuity at that time was R.E.: 6/12 (20/40); L.E.: 6/15 (20/50). The corneas of both eyes contained numerous crystals that were known to have been present for 13 years (Fig. 1). The anterior stroma of the central portion of each cornea was thought to be filled with a multitude of fine crystals. The deeper stroma and the corneal endothelium were normal. Crystals were not identified in the conjunctiva. The remainder of the eye examination showed no abnormalities. Because the corneal crystals were considered to be the cause of visual impairment, a lamellar keratoplasty was performed.

Investigations at that time revealed a hemoglobin count of 11.4 g/100 ml, a hematocrit level of 35%, a total serum protein of 9.1 g/100 ml (albumin, 3.6%; gammaglobulin, 3.9 g/100 ml). Serum protein electrophoresis on cellulose acetate membrane revealed a large monoclonal spike (M component) in the gamma area. Immunoelectrophoresis on agarose gel using heavy and light chain-specific antisera identified the M component as IgG with kappa light chains. Bence-Jones protein was not present in the urine. Because of insufficient quantities of protein, immunoglobulins in the tears could not be detected by immunoelectrophoresis. A right iliac bone marrow biopsy was normal in cellularity with good maturation of both the erythroid and myeloid series. A plasmacytosis of 21% was present with sheets of plasma cells scattered diffusely throughout the marrow. The megakaryocytes and bony spicules appeared normal. A skeletal survey disclosed a partial collapse of the third lumbar and twelfth thoracic vertebrae, diffuse osteoporosis with degenerative changes in the spine, and multiple motheaten areas of destruction in several metatarsals and phalanges of the right foot. Once the diagnosis of multiple myeloma was made, the patient began receiving melphalan and prednisone.

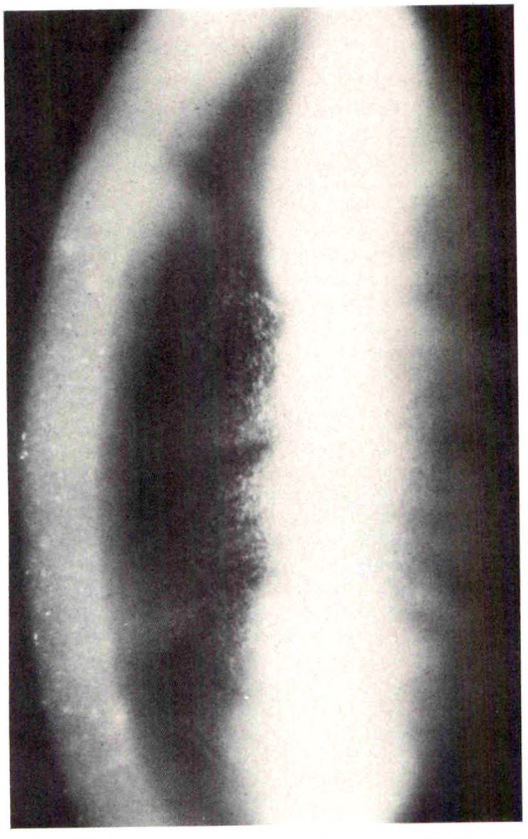


Fig. 1 (Klintworth, Bredehoeft, and Reed). Case 1. Slit-lamp photograph of cornea showing crystals.

The crystals appeared in the regenerated epithelium of the grafted left eye, but they gradually decreased in both corneas after the patient had been receiving chemotherapy for several months, which coincided with the gradual diminution in the serum gammaglobulin. A clear area developed in the visual axis of the right eye with improvement in visual acuity to 6/6 (20/20). The best corrected visual acuity in the left eye was 6/24 (20/80) as the result of persistent crystals and graft astigmatism.

The patient's general condition also improved with therapy, and she began to walk with little difficulty. By February 1977, the bone marrow contained less than 1% plasma cells. The serum gammaglobulin gradually decreased, and in August 1977, the serum total protein, gammaglobulin, and M components were 6.9, 0.2 and 1.3 g/100 ml, respectively.

Case 2—A 59-year-old man was noted to have crystals in the corneas of both eyes on routine eye examination in 1967. Although these crystals apparently increased in number, they hardly affected the vision until 1972 when the patient was referred here. At that time, his best corrected visual acuity in each eye was 6/18 (20/60). Fine crystalline deposits were distributed equally and diffusely in both corneas on slit-lamp examination (Fig. 2). These were thought to be in the epithelium, possibly in Bowman's membrane, but not in the corneal stroma. In both corneas, the superior portion appeared to have been spared. Numerous iridescent punctate opacities were located in the anterior and posterior cortices of both lenses, but not in the nuclear portions (Fig. 3). The slight haziness of the cornea and lens produced by the opacities made it difficult to see fine detail on ophthalmoscopy, but some pigment dispersion and clumping was present in the left macula.

The patient had a history of bilateral tenderness of his feet and chronic discomfort in the joints since 1967.

In 1972 analyses of the serum disclosed a total protein of 8.3 to 9.3 g/100 ml, 5.7 g/100 ml globulin, and 3.6 to 4.2 g/100 ml of an anomalous gammaglob-



Fig. 2 (Klintworth, Bredehoeft, and Reed). Case 2. Slit-lamp photograph of cornea showing crystals.

ulin, which was found on immunoelectrophoresis to be IgG kappa. The serum albumin and uric acid levels were normal, and so was a complete blood cell count. Urine was negative for protein. A sternal marrow contained 5 to 10% pleomorphic plasma cells and only a trace of stainable iron. Multiple myeloma was diagnosed and on Nov. 20, 1972, a 24-month course of melphalan (15 mg/day in a single dose for four days, every 28 days) and prednisone (75 mg/day for seven days, every month) was initiated. Forty milliliters of iron dextran was injected intravenously for the iron deficiency in the marrow.

After five months' treatment, 3 to 5% of the cells in the sternal bone marrow were plasma cells. Occasional binucleated, trinucleated, and multinucleated plasma cells were noted, some of which had clefted nuclei. A normal amount of iron was present. A skeletal survey disclosed diffuse osteoporosis, but no characteristic lesions of myeloma. The patient had one episode of epistaxis in September 1973 associated with a reduction in circulating platelets (about 120,000/ml). In November 1974, after chemotherapy was discontinued, the patient felt well and had a residual M component of 0.9 to 1.5 g/100 ml, and a marrow aspirate showed 2 to 3% plasma cells with occasional abnormal forms. He had some lower spine pain for approximately six weeks in January and February 1977. Otherwise, he was well without bone pain, infections, fever, a bleeding tendency, or bruisability. On April 12, 1977, a sternal bone marrow aspirate contained approximately 14% plasma cells, most of which appeared normal, but some were binucleated, and a decreased number of megakaryocytes (only two to three were seen on the entire smear).

Following removal of a portion of the corneal epithelium in 1972, crystals recurred in the regenerated epithelium. After eight months of chemotherapy, the crystals began to disappear first in the cornea, then in the lens. They had completely disappeared after the 24 months of chemotherapy and had not recurred in August 1977 when the vision returned to 6/6 (20/20) in each eye.

Results

The tissue examined consisted of biopsy specimens of conjunctiva from both individuals, minute fragments of corneal

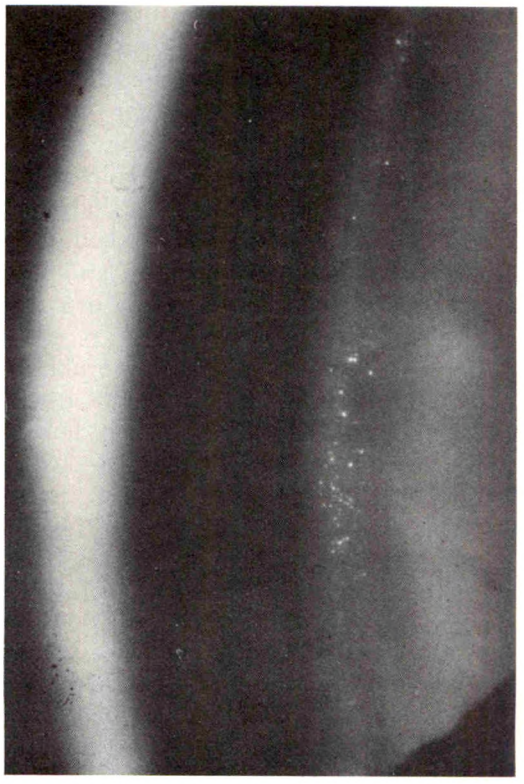


Fig. 3 (Klintworth, Bredehoeft, and Reed). Case 2. Refractile punctate opacities in anterior cortex of lens.

epithelium from the patient in Case 2, the lamellar keratoplasty specimen from the patient in Case 1, and bone marrow smears from both patients.

Because the nature of corneal crystals in hypergammaglobulinemias was uncertain, the corneal button obtained at lamellar keratoplasty from the patient in Case 1 was cut into four equal portions immediately after excision. One piece was fixed in buffered formalin, another in absolute ethanol, a third in 4% cacodylate buffered glutaraldehyde (pH 7.2), and a fourth was rapidly frozen in liquid nitrogen. The unfixed frozen tissue was sectioned with a cryostat and mounted on gelatin-coated glass slides. The formalin and absolute alcohol-fixed material was embedded in Paraplast and processed in the usual manner. The tissue placed in absolute alcohol was transferred directly to xylol and then to Paraplast; the formalin-fixed cornea was first dehydrated through graded alcohols. Unstained and stained corneal tissue was examined by regular optical, phase contrast, and fluorescent microscopy. The stains used included hematoxylin and eosin, PAS, Masson trichrome, Congo red, methenamine silver technique for urates, Ninhydrin-Schiff, and the Sloper technique for cystine and proteins with disulphide bonds.

Because the corneal crystals probably contained immunoglobulins, the direct immunofluorescent and indirect immunoperoxidase sandwich techniques were employed. The presence of IgG, IgM, IgA, albumin, fibrinogen, and the C3 component of complement was sought by the direct immunofluorescent technique using 2- to 4-μ thick frozen sections of corneal tissue on gelatin-coated slides and specific fluorescein-labeled antisera. Paraplast-embedded and fresh unfixed tissue was studied by the immunoperoxidase indirect sandwich technique for identification of immunoglobulins. The Paraplast sections (8 μ thick) were deparaffinized in the standard fashion by using xylene. The fresh-frozen tissue was cut at 2 to 4 μ by standard techniques and placed on gelatin-coated slides. Phosphate-buffered saline 0.5 M, pH 7.6, was used for all dilutions and in the other steps indicated. The sections were washed three times in phosphate-buffered saline (five minutes per wash). Sections were then incubated for one hour at 22° C with primary antibodies in a moisture chamber. The primary antisera applied included: goat antihuman polyvalent IgG/IgA/IgM (precipitin titer 1:32), goat antihuman IgG (H and L chain) (titer 1:64), goat antihuman IgG; IgG fraction (titer 1:32), goat antihuman kappa light chain IgG fraction (titer 1:32 and 1:2), goat antihuman lambda light chain IgG fraction (titer 1:2 and 1:32), and goat antihuman IgM (precipitin titer 1:8). Control slides included lymph nodes and kidneys from patients with multiple myeloma. Because Paraplast reduces diaminobenzidine by itself, the tissue sections embedded in it were first soaked with undiluted normal human serum to bind most of the nonspecific precipitation.

After incubation with the primary antibodies, the slides were washed three times with phosphate-buffered saline (five minutes per wash). In the moisture chamber, the sections were incubated for one hour in horseradish peroxidase conjugated rabbit antigoat IgG (IgG fraction) (titer 1:4). The sections were then washed three times in phosphate-buffered saline. The specific sites of antibody binding were determined with a diaminobenzidine reaction, which yields a deep brown color at locations with positive reactions. The reagent for this test was prepared immediately before use by dissolving 3,3′-diaminobenzidine tetrahydrochloride (25 mg/100 ml) in 0.01M Tris (pH 7.4) followed by the addition of hydrogen peroxide (0.05%). Sections were

incubated with this reagent for one hour at 28° C, then washed three times with phosphate-buffered saline. Duplicate sections as above were exposed in 1% collidine-buffered osmium tetroxide (pH 7.4) for five minutes at 22° C and then mounted with glycerol. After examination of the sections, areas were photographed, the coverslips were removed, and the sections counterstained with hematoxylin, dehydrated, and mounted.

The glutaraldehyde-fixed tissue was postfixed with 1% osmium tetroxide and embedded in Epon for electron microscopy according to standard procedures. Sections 50 nm thick were examined by transmission electron microscopy without staining and after staining with uranyl acetate, lead citrate, or both. A beam of monochromatic light of 633-nm wave length was passed through photographic negatives of electron micrographs of the corneal crystals according to basic principles of light diffraction.[6]

The lamellar keratoplasty specimen of the patient in Case 1 consisted of epithelium, Bowman's zone, and the superficial corneal lamellae. The crystals observed clinically were located exclusively within the corneal epithelium, despite the clinical impression that the superficial stroma was also involved (Fig. 4). They were elongated and of variable length (up to 32.5 μ) and width (up to 7.5 μ). In some areas numerous crystals extended throughout the entire thickness of the corneal epithelium, whereas in other regions they were limited to the superficial or deep layers of the epithelium. By light microscopy the crystals appeared to occupy both intra- and extracellular positions. Cross-sectional profiles were hexagonal, but when cut in longitudinal sections, their sides were parallel. The crystals were eosinophilic and PAS- and Ninhydrin-Schiff-positive. They appeared a brilliant red with the modified Masson trichrome stain (containing the red dyes Ponceau 2R, acid fuchsin, and azophloxine), weakly positive with the Sloper technique, and did not stain with Congo red or methenamine silver. The crystals did not manifest birefringence or autofluorescence, and were not soluble in aqueous solutions, ethanol of variable concentrations, or xylol.

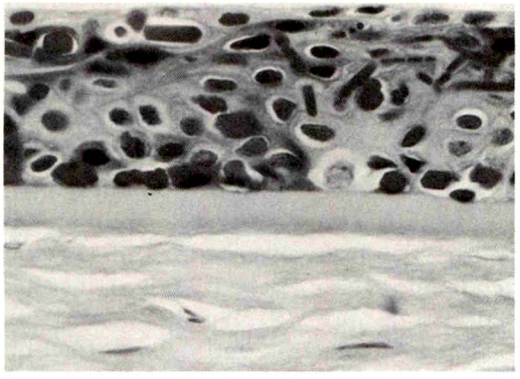


Fig. 4 (Klintworth, Bredehoeft, and Reed). Crystalline deposits sectioned at variable depths in the corneal epithelium (Masson trichrome, ×680).

Direct immunofluoresent examination with gamma chain-specific antisera showed circumscriptal localization about lacunae within the epithelium, normal staining of the epithelial basement membrane, and a questionable increased localization in the corneal epithelium. There was no significant localization for alpha or mu chain, complement component C3, fibrinogen, or albumin. With the immunoperoxidase indirect sandwich technique, some corneal crystals reacted positively, especially at their periphery with antisera against human polyvalent immunoglobulins (IgG/IgA/IgM), IgG and IgG kappa (Fig. 5). The location of the reaction product was mainly around crystals in the deeper cornea and also occurred on the surface of the corneal epithelium.

When viewed by transmission electron microscopy, the corneal crystals were barely visible in unstained preparations, but much more discernible after staining with uranyl acetate and lead citrate. Some

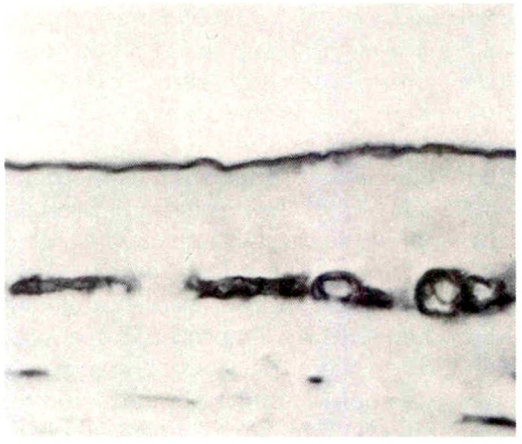


Fig. 5 (Klintworth, Bredehoeft, and Reed). Positive immunoperoxidase reaction to IgG around crystals in deeper portion of corneal epithelium and on the surface of the cornea. This is a portion of the cornea different from that illustrated in Figure 4 (unstained, ×680).

crystalline profiles were hexagonal in cross-section with crisp edges (Fig. 6). Because of their extreme electron density in stained preparations, resolution of surrounding membranes could not always be made, but they appeared to be both between and within epithelial cells (Figs. 6-9). Some intracytoplasmic deposits had contours of varying irregularity, at times associated with apparently nonattached rounded globules of similar material lying adjacent to larger inclusions within the cytosol (Fig. 8). In some crystals a fine internal periodicity could be resolved under high magnification (Figs. 9 and 10). By calibrated measurement, the spacings between the linear electron densities were approximately 10 to 11 nm apart. Using the principle that in-phase wave energies impinging on a periodic structure yield an interference pattern produced by summation and cancellation of wave energies, we established a diffraction pattern confirming the internal periodicity of the crystals by passing the beam of light of 633-nm wave length from the ruby laser through negatives of electron micrographs of 50-nm thick sections of these crystals. Because of the random orientation of the thin section electron micrographs, we could not establish the lattice conformation and orientation of the crystalline subunits.

Crystals were not identified in a biopsy specimen of the conjunctiva from the patient in Case 1, or in minute fragments of corneal epithelium and conjunctiva excised from the patient in Case 2. Plasma cells were not present in any of the ocular tissues examined. Crystals were not identified in plasma cells of the bone marrow of either case.

Discussion

The rarity of corneal crystals in hypergammaglobulinemia and the difficulty in identifying them in small biopsy specimens, as exemplified in this study, have heretofore impeded their identification. In Markoff's[7] patient, the crystals appeared during urethane therapy, and disappeared when the drug was discontinued, suggesting a causal relationship to the therapeutic agent. However, other patients have developed corneal crystals in the absence of medication. The clinical resemblance of the crystals to cholesterol and the difficulty in seeing them in excised tissues suggested they might be composed of lipid that dissolved during histologic processing. Although not identifying the crystals with certainty, Aronson and Shaw[2] suggested cholesterol. This interpretation was based on positive digitonin and Schultz reactions and Maltese crosses in polarized light on formalin-fixed and frozen portions of conjunctival tissue. This view gained additional support by observations of Laibson and Damiano[3] who studied conjunctival and corneal biopsies and a sternal marrow aspirate by electron and x-ray diffraction. They concluded that the crystals were cholesteryl stearate, but like Aronson and

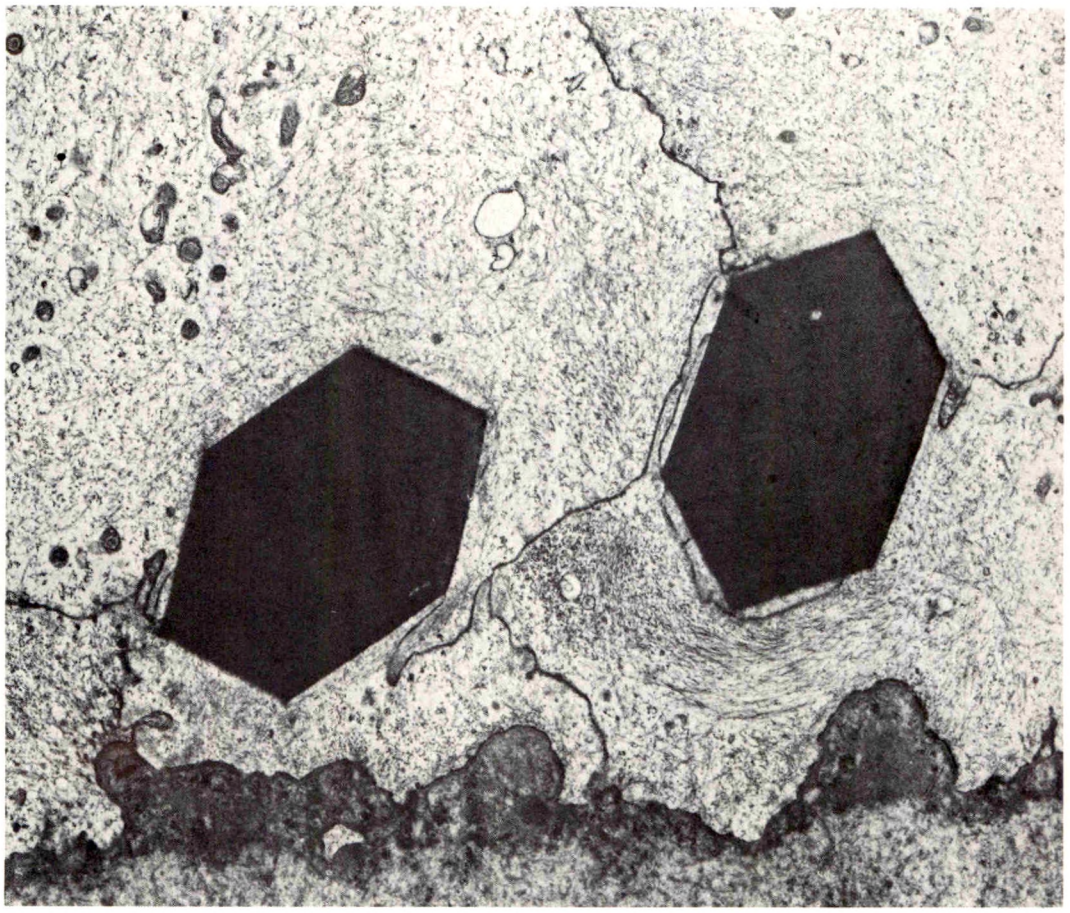


Fig. 6 (Klintworth, Bredehoeft, and Reed). Hexagonal profiles of crystals in basal portion of corneal epithelium (×10,000).

Shaw[2] they did not conclusively illustrate what they analyzed. On the other hand, Pinkerton and Robertson[4] provided the first morphologic observations of the corneal crystals and concluded that they were not composed of lipid, but protein, and were identical to those found elsewhere in individuals with plasma cell dyscrasias. Our findings concur with this conclusion and support the belief that the crystals are composed of immunoglobulin. Other observations corroborate this view. Since Glaus'[8] first description in 1917 of intra- and extracellular crystals in multiple myeloma, crystalline deposits have been reported many times in this disease and in other plasma cell dyscrasias. Intracytoplasmic crystals or paracrystalline structures have been identified within plasma cells[2,4,9–13] in areas infiltrated by these cells. They have also been found in the kidney. The corneal crystals in our study are strikingly similar morphologically to those observed in the cytoplasm of neoplastic or reactive plasma cells,[4,11,12,14,15] crystallized plasma gammaglobulins,[16,17] and to the crystals observed in renal tubular epithelium in multiple myeloma.[11] In this regard, three patients with hypergammaglobulinemic

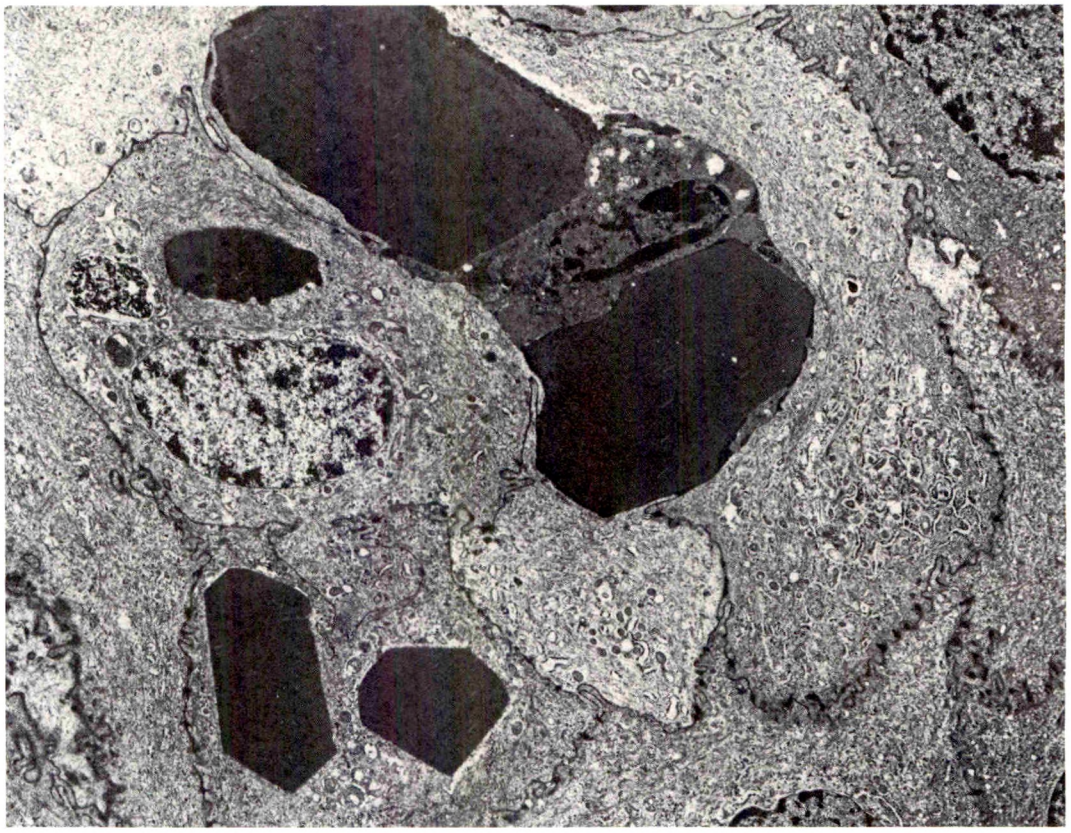


Fig. 7 (Klintworth, Bredehoeft, and Reed). Variable configurations of crystalline deposits in corneal epithelium. Some of the electron dense material appears to be intracellular (×5,300).

corneal crystals have had crystalline inclusions within plasma cells of the bone marrow.[2-4]

Related conditions that have an excessive proliferation of a single clone of immunoglobulin-producing cells are variably referred to as plasma cell dyscrasias, monoclonal gammopathies, dysgammaglobulinemias, and paraimmunoglobulinopathies. These abnormal proliferations of plasma cells may be neoplastic or reactive to a wide variety of antigenic stimuli. The underlying disease in other reported cases of corneal crystals with plasma cell dyscrasias was designated multiple myeloma ,[1,2] dysproteinemia,[4] or paraproteinemia.[3] The latter two terms, which imply the existence of abnormal proteins, no longer serve a useful purpose. In our patients the quantity of monoclonal hypergammaglobulinemia coupled with more than 5% bone marrow plasma cells supports the diagnosis of multiple myeloma.[16-18] However, both cases were associated with a relatively benign course even before the advent of therapy. Arthralgia that eluded diagnosis was a prominent symptom; nonocular physical findings were conspicuously absent; patients were not prone to infections, undue sensitivity to cold, hemorrhagic or hyperviscosity manifestations; plasma cells were not identified in peripheral blood smears.

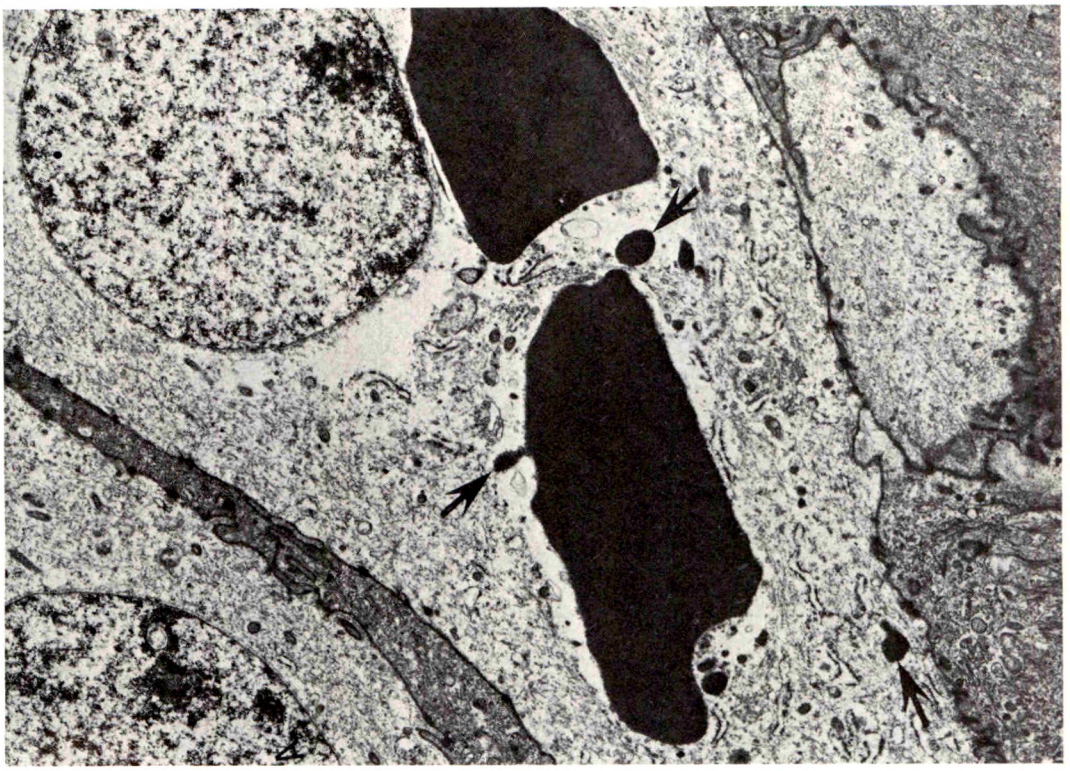


Fig. 8 (Klintworth, Bredehoeft, and Reed). Smaller globules of electron dense material (arrows) are associated with larger irregularly shaped intracellular profiles (×7,400).

An understanding of the reason for spontaneous gammaglobulin crystallization in the cornea clearly has broad biologic importance. Not only is spontaneously crystallizing gammaglobulin uncommon,[19] but the crystallinization of intact molecules of immunoglobulins poses difficulties.[20] Both of our patients as well as the patient of Liabson and Damino[3] were associated with IgG kappa chains. Also Bence-Jones proteinuria has been absent in all documented cases with corneal crystals.

In theory, the corneal crystals of the patient in Case 1 could have arisen from the tears, from the corneoscleral limbal vasculature or from plasma cells in the conjunctiva. Because the crystals were localized in the corneal epithelium and tears contain immunoglobulins, gammaglobulin might have crystallized in the tears. Numerous plasma cells were not noted in the conjunctiva, and unlike in the patient reported by Pinkerton and Robertson,[4] the crystals in the patient in Case 1 did not stem from a tissue infiltration by cells with cytoplasmic crystals. The crystals observed in ocular tissue by Pinkerton and Robertson[4] were exclusively within the cytoplasm of cells. Their observations and ours support the theory that crystals occur in ocular tissues either by an infiltration of plasma cells with crystalline inclusions or by the spontaneous crystallization of immunoglobulins, or both. The occurrence of corneal crystals is sometimes preceded by episodes of conjunctivitis or anterior uveitis,[1,2,4]

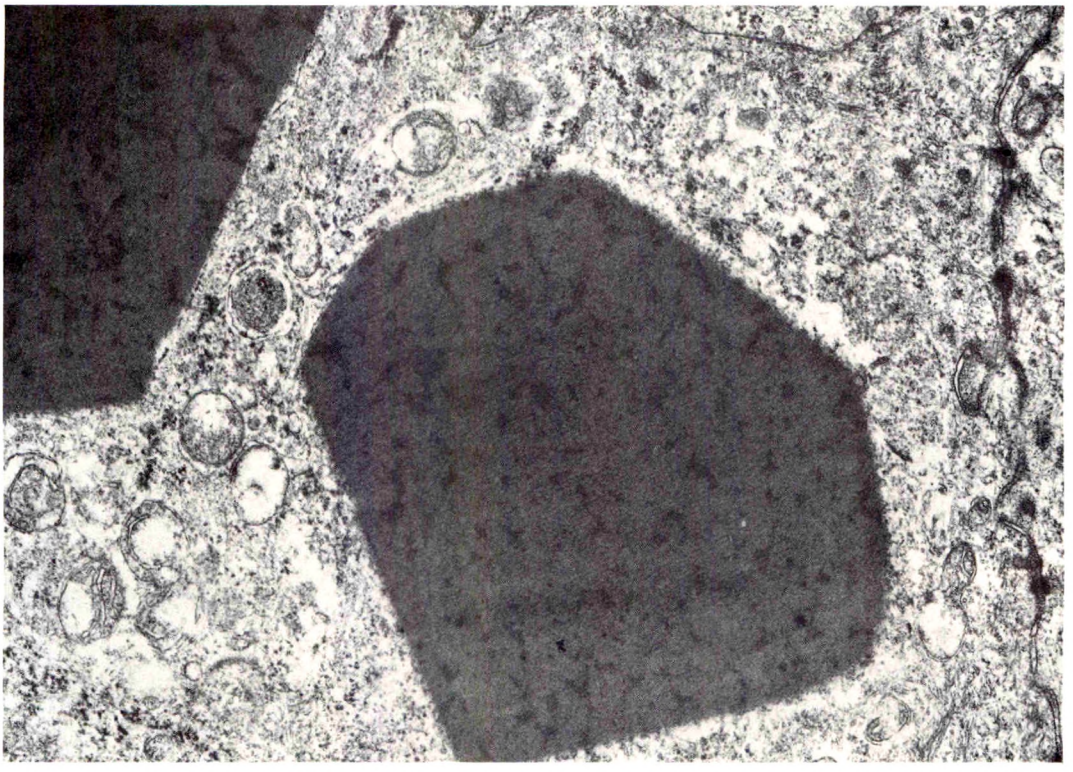


Fig. 9 (Klintworth, Bredehoeft, and Reed). Intracellular crystalline deposit with regular internal periodicity (×19,500).

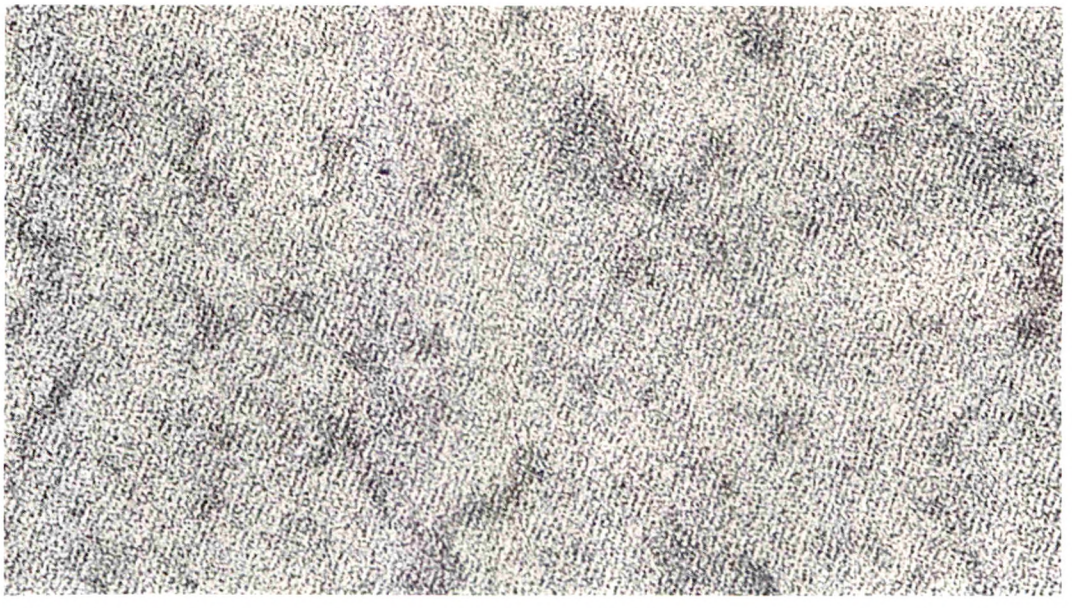


Fig. 10 (Klintworth, Bredehoeft, and Reed). Higher magnification of electron dense material in Figure 9 showing a periodic inner structure (×83,300).

which perhaps provide an increased number of crystalline-containing plasma cells.

Summary

A 46-year old woman and a 59-year-old man had corneal crystals, multiple myeloma, and IgG kappa hypergammaglobulinemia. In one case, crystalline deposits were also present in the lens. In both patients there was a marked decrease in the amount of crystals during chemotherapy. The crystals within the cornea of one case were identified by light and electron microscopy in material obtained during a lamellar keratoplasty. The crystalline deposits were located only in the corneal epithelium, and their regular repeating internal arrangement was confirmed by monochromatic optical diffraction of electron micrographs of sections through them. By immunofluorescent and immunoperoxidase techniques, the crystals reacted positively for immunoglobulin and particularly IgG kappa chains.

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THE HLA ANTIGENS IN COGAN'S SYNDROME

MURIEL I. KAISER-KUPFER, M.D., KAMAL K. MITTAL, PH.D.,
LUIS A. DEL VALLE, M.D., AND BARTON F. HAYNES, M.D.
Bethesda, Maryland

The significant association of some diseases and certain histocompatibility (HLA) antigens has been previously reported.[1] Such correlations have a diagnostic as well as a prognostic value for some of these diseases. In 1975, Char, Cogan, and Sullivan[2] suggested a positive association of HLA-B17 with nonsyphilitic interstitial keratitis and vestibuloauditory dysfunction (Cogan's syndrome) by observing B17 in three of the four patients studied. A subsequent report[3] confirmed this association in another patient, whereas another report[4] questioned these findings because of the absence of B17 in another patient.

We report herein the HLA typings in ten patients, all with a well-documented diagnosis of Cogan's syndrome in which it was not possible to establish an association of B17 with this disease.

SUBJECTS AND METHODS

Four hundred sixty-nine apparently healthy, unrelated white persons from the Washington, D.C., metropolitan area were typed for the HLA and ABO antigens as the control group. Ten white patients with nonsyphilitic interstitial keratitis and vestibuloauditory dysfunction (Cogan's syndrome) were studied clinically and typed for the HLA antigens in a double-masked fashion.

These patients all conformed to the established criteria of the syndrome including a history of active nonsyphilitic recurrent interstitial keratitis, vestibular symptoms, and evidence of a sensoryneural hearing loss. Five of the ten patients were Jewish (Table 1).

All individuals were tested for the 40 HLA antigens of the loci A, B, and C by the standard lymphocyte microcytotoxic test.[5] To determine the significance of differences in phenotype frequencies of antigens between healthy controls and patients, the P values were computed by using the Fisher's exact probabilities from the distribution of the chi-squares.

RESULTS

The ABO and HLA phenotypes in the ten patients are shown (Table 1). Only one patient, No. 10, had B17. Phenotype frequencies of those antigens in which the P value was less than .05, in addition to those of B17, which was not significantly different between the two groups, is shown (Table 2).

DISCUSSION

Although the present series is still small, it represents the largest group of patients with Cogan's syndrome who have had HLA typing. This series clearly indicates that no relationship exists between this disease and HLA-B17 antigen. Furthermore, although three antigens, A9 (Aw24), Bw35, and Cw4 appear to have an increased frequency in this disease, the small sample size precludes interpret-

From the Clinical Branch, National Eye Institute, National Institutes of Health (Drs. Kaiser-Kupfer and Del Valle); the Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Disease, National Institutes of Health (Dr. Haynes); and the Bureau of Biologics, Food and Drug Administration, Department of Health, Education, and Welfare (Dr. Mittal), Bethesda, Maryland.

Reprint requests to Muriel Kaiser-Kupfer, M.D., National Eye Institute, Building 10, Room 2D12, National Institutes of Health, Bethesda, MD 20014.

TABLE 1

ABO AND HLA PHENOTYPES OF TEN PATIENTS WITH COGAN'S SYNDROME

Patient No.	Sex	Age (yrs)	ABO Type	HLA Phenotype
1*	F	59	B	Aw31, Aw32; B18, Bw35; Cw4
2†	F	48	O	Aw24, Aw30; B13, B14; —
3	F	35	O	A2, A9; Bw21, —; —
4	F	30	O	Aw24, Aw33; B7, Bw35; Cw4
5*†	F	28	A	A2, A28; B7, Bw39; —
6*†	F	28	O	A3, Aw24; Bw38, Bw35; Cw4
7†	F	26	A	A25, A28; B18, Bw35; Cw4
8	M	25	A	A1, A2; B8, B15; Cw3
9*†	F	20	B	A2, A9; B12, Bw41; Cw4
10	F	18	A	A3, Aw32; B17, Bw35; Cw4

*Patients previously examined by Char, Cogan, and Sullivan.[2]
†Jewish.

ing the significance of these increases in phenotype frequencies.

In an effort to reconcile these data with those of Char, Cogan, and Sullivan,[2] we re-examined all four patients included in their report (Table 1). However, on extensive testing in our laboratory, none of these four patients were found to have B17. Additionally, two of the patients who had been reported to have B17 by Char, Cogan, and Sullivan[2] were typed in a masked fashion by independent outside laboratories. These investigators also failed to confirm the presence of B17 and confirmed the precise HLA typing. This experience reaffirms the need for caution not only in the interpretation of data from few patients, but also in the accuracy of the tissue typing performed.[5]

SUMMARY

HLA typing of ten patients with well documented Cogan's syndrome failed to support previous reports of an increased

TABLE 2

SELECTED COMPARISONS OF PHENOTYPE FREQUENCIES IN COGAN'S SYNDROME

HLA Antigen	Normal (No.=469) Phenotype Frequency (%)	Cogan's Syndrome (No.=10) Phenotype Frequency (%)	Exact P Value
HLA-A9 (or Aw24)	19.83	50.00	0.0343*
HLA-B17	9.17	10.00	1.0000
HLA-Bw35	20.47	50.00	0.0388*
HLA-Cw4	18.34	60.00	0.0047*

*Less than .05.

incidence of HLA-B17. Although HLA-A9 (Aw24), Bw35, and Cw4 appeared increased in frequency among patients, the small number of cases precluded attaching importance to the significance of these increased frequencies.

ACKNOWLEDGMENTS

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D. M. Fotino, M.D., of the New York Blood Center, Inc., and H. A. Perkins, M.D., of the Irwin Memorial Blood Bank of the San Francisco Medical Society, independently typed the patients in this study.

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OPHTHALMIC MINIATURE

The body's lamp is your eye. When your eyes are in focus (i.e., on a single object), your whole body is distinctly guided; but when they are crossed (i.e., with one eye on one thing, the other on another, or trying to keep an equal eye on two masters), your body is "in the dark." See to it, then, that your "light" isn't "night." For if your whole being is illuminated, without any part reserved for darkness, you'll be as completely lit up as when a flash of lightning shines on you.

Clarence Jordan, *The Cotton Patch Version of Luke and Acts*
New York, Kainonia; Association Press

THE CORNEAL ENDOTHELIUM AND THE SPECTRUM OF ESSENTIAL IRIS ATROPHY

DAVID G. CAMPBELL, M.D., M. BRUCE SHIELDS, M.D., AND TAYLOR R. SMITH, M.D.

Boston, Massachusetts

The cause of the pupillary displacement and the peripheral anterior synechiae in the spectrum[1] of essential iris atrophy (progressive essential iris atrophy and Chandler's syndrome[2]) has not been elucidated. The two most frequently advanced theories have been: (1) that spontaneous hole formation in the iris allows the pupil and iris to drift to the opposite side, causes the corectopia, and allows the peripheral anterior synechiae to develop,[3-5] or (2) that the peripheral anterior synechiae develop first and pull the pupil toward the synechiae.[1,6-9] The primary purpose of this report is to endorse the latter theory, to propose the hypothesis that corneal endothelial degeneration and growth of an ectopic membrane are the primary pathophysiologic events in the spectrum, and to explain the entire syndrome.

Recently, iris nodules were described in this spectrum[10]; they had been present, but not emphasized, in past pathologic descriptions.[11-13] Cogan and Reese,[14] who first described these nodules and their association with an ectopic endothelial membrane (Descemet's membrane), and Scheie and Yanoff[15] classified patients with these nodules in a separate category. Because our cases shared the findings of endothelial degeneration, peripheral anterior synechiae, corectopia, ectropion uveae, glaucoma, and either partial or complete iris atrophy,[10] we proposed that they be classified in the spectrum of essential iris atrophy. We demonstrate herein that these nodules are caused by the membrane and serve as a clinical marker for it.

From the Howe Laboratory of Ophthalmology of Harvard Medical School at the Massachusetts Eye and Ear Infirmary, Boston, Massachusetts. This study was supported by National Eye Institute Grant 5R01-EY 00002 and by private donations.

Reprint requests to David G. Campbell, M.D., Department of Ophthalmology, Emory University Clinic, 1365 Clifton Rd., N.E., Atlanta, GA 30322.

MATERIAL AND METHODS

In addition to the charts of 82 patients with essential iris atrophy, we[16] studied the pathology specimens of ten enucleated eyes with essential iris atrophy obtained from the pathology laboratory at the Massachusetts Eye and Ear Infirmary. A previous report[3] described five of the eyes and the Cogan and Reese report[14] described a sixth eye. A map of the extent of overgrowth of the iris by the endothelial membrane in this eye was constructed with serial sections to evaluate the location of the ectopic endothelial membrane in relation to the nodules.

The following case manifests the entire spectrum in one eye.

CASE REPORT

A 36-year-old man had blurring of vision, distortion of the left pupil, and a right esotropia with amblyopia (Fig. 1, A). Visual acuity was R.E.: 6/60 (20/200); L.E.: 6/6 (20/20). The right eye was otherwise normal. The Descemet's membrane of the left eye had an iridescent quality. There were prominent, yellowish synechiae to the cornea at the 12, 3, 6, and 9 o'clock meridians. There were areas of iris atrophy with one complete hole. The pupil was enlarged and slightly displaced temporally. There was ectropion uveae temporally. The iris was lifted anteriorly off the lens surface. Gonioscopy revealed six hours of angle closure or obscuration. Small yellow nodules, like wool balls on a sweater, appeared on portions of the iris surface. The intraocular pressure was: R.E.: 13 mm Hg; L.E.: 19 mm Hg. The tonographic facility of outflow (C) was: R.E.: 0.48; L.E.: 0.33. The left physiologic cup was wider than the right cup. The fields were full. Thirty months later, in the left eye, the intraocular pressure was 40 mm Hg, and the C had decreased to 0.13. The gonioscopic appearance had barely changed. The

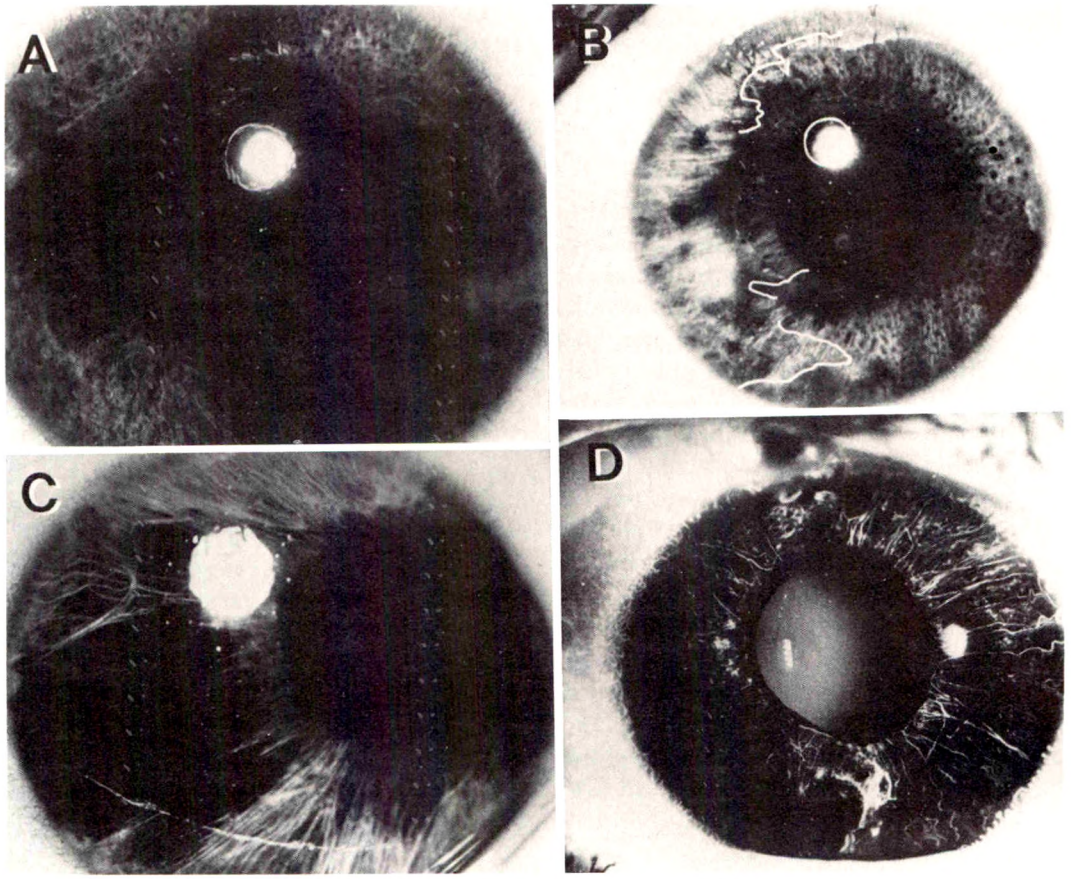


Fig. 1 (Campbell, Shields, and Smith). A, Iris nodules and a melting hole at 3 o'clock meridian in a 36-year-old man. B, Left eye with temporal nodules covered by endothelial membrane; white line represents leading edge of membrane. C, A stretch hole. D, Fluorescein iris angiogram showing collateral vessels around a melting hole at 6 o'clock meridian.

decrease in C was postulated to be caused by an overgrowth of the angle by an endothelial membrane. Endothelial degeneration became increasingly apparent with central granular thickening. The epithelium occasionally became edematous at pressures in the 20 to 30 mm Hg range. The iris nodules appeared over the entire iris surface.

Results

The clinical survey of 82 patients showed that there could be an overlap between the two ends of the spectrum: some patients with Chandler's syndrome progressed to hole formation in the iris, whereas many with progressive essential iris atrophy showed signs of endothelial disease. These findings indicated that endothelial degeneration was common throughout the spectrum.

The pathologic review of ten whole eyes enucleated with a diagnosis of essential iris atrophy revealed that three eyes had iris nodules. A nodule was always associated with a surrounding or overlying endothelial membrane, which supports two previous reports.[14,15] A map of the extent of the membrane coverage made in one eye with iris nodules (Fig. 1, B) showed that the nodules indicated the presence and, in this eye, the extent of the membrane. These findings suggested that the membrane caused the development of

these unusual protuberances. Microscopy revealed that the nodules nearest the periphery of the iris, which had clinically appeared to be smooth and pedunculated, were completely covered by the membrane (Fig. 2, A), whereas the nodules closer to the leading edge of the membrane, which were flatter, were only partially covered (Fig. 2, C and D). Nodules at the leading edge were not covered by the membrane at all, but were surrounded by it, which suggests that a cluster of iris stromal cells, at first sessile and flat, were surrounded by the membrane and isolated in islands at the leading edge. Later, the membrane apparently grew up around the iris cells and raised them into pedunculated forms. Although nodules indicated a membrane, an absence of nodules did not indicate an absence of the membrane in other eyes. The majority of irides covered with membranes did not have nodules. Three eyes in previous studies also had nodules with essential iris atrophy, all associated with membrane.[11–13]

Pathologic review revealed that all ten eyes had evidence of minor or major aber-

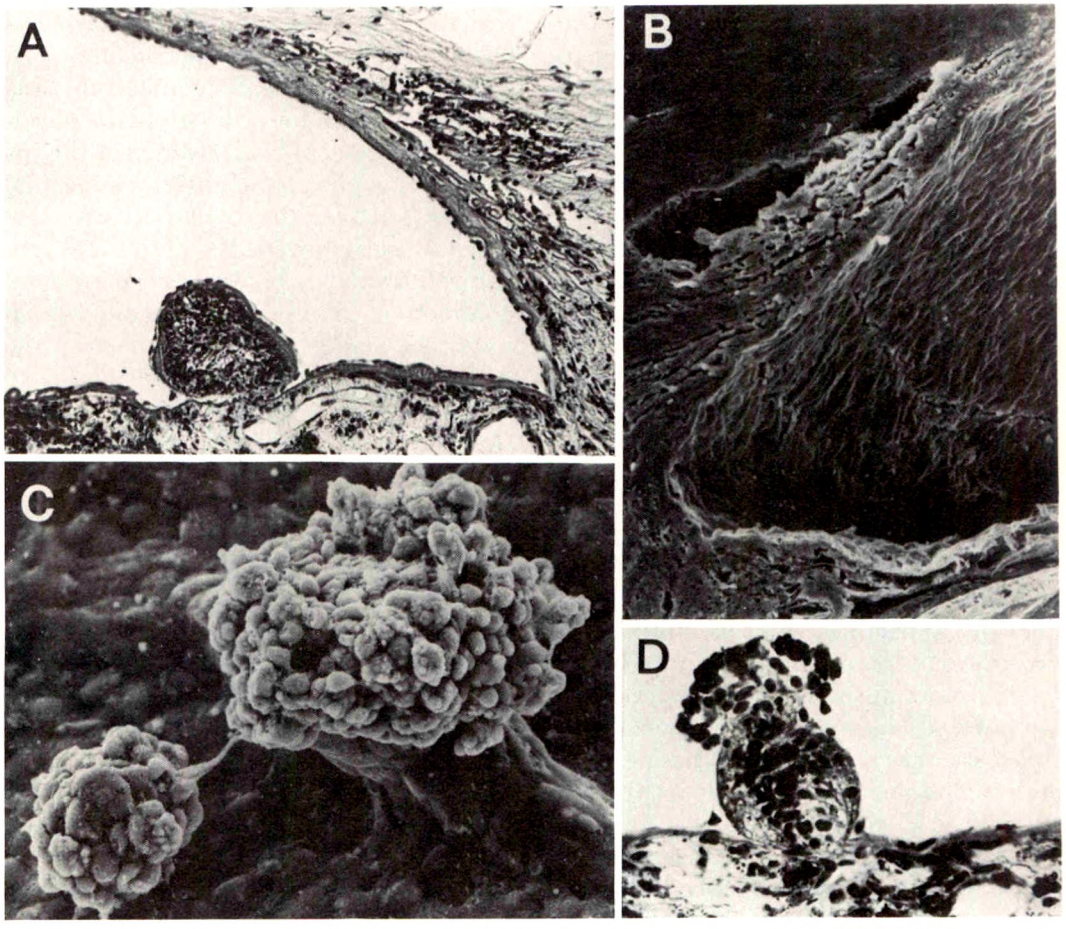


Fig. 2 (Campbell, Shields, and Smith). A, Endothelial membrane over open angle with totally covered iris nodule (PAS, × 275). B, Scanning electron micrograph of open angle covered by ectopic endothelial membrane (× 200). C, Scanning electron micrograph of iris covered by endothelium with partially covered nodule (× 1000). D, Iris nodule partially covered by membrane (PAS, × 400).

rant endothelial overgrowth onto the surface of the iris (Fig. 2, A), which has been reported,[6,8,9,11-13,16-21] although it is thought to be rare. This correlated with the clinical finding that endothelial degeneration is common.[2,22-24] Diseased corneal endothelium tends to proliferate in some instances.[26]

Previously it was thought that peripheral anterior synechiae had to form before an endothelial membrane could overgrow onto the iris.[27] Reports, however, have shown an open angle overgrown by an endothelial membrane in essential iris atrophy[3,9] and in the Cogan-Reese syndrome.[14,15,28] Six of ten eyes in our study had sections showing overgrowth of an open or partially open angle by an endothelial membrane (Fig. 2, A), which indicates that this event commonly occurs in essential iris atrophy and that overgrowth can occur in the absence of synechiae and before their development.

Chandler and Grant[1] stated that the degree of glaucoma usually corresponded to the degree of synechial closure of the angle, which was generally true in our clinical survey. Some patients, however, had marked glaucoma and few peripheral anterior synechiae. The overgrowth of this biomicroscopically unseen membrane probably accounted for this discrepancy. This was proven pathologically in one eye (Fig. 1, B) that had only one sixth of the angle closed by peripheral anterior synechiae, but an intraocular presure of 50 mm Hg and whose fellow eye was normal and nonglaucomatous. By studying serial sections, the open angle in this case was found to be lined by an endothelial membrane for almost 360 degrees (Fig. 2, B).

Knowing that endothelial degeneration and ectopic endothelial proliferation over an open angle were common in this spectrum, we sought evidence that the endothelial membrane then contracted and caused the peripheral anterior synechiae. Unfortunately, in the areas of adhesion, often old, we could not determine whether the two membranes on the corneal side and on the iris side had fused. Occasionally, however, there appeared to be a double membrane and a contraction at the leading edge, which corroborated similar findings of Pau.[20] Also suggestive of contraction were two areas in two eyes where spaces between the iris and the cornea existed within peripheral anterior synechiae. In these areas, two membranes existed, suggesting that the endothelium had first overgrown and then contracted.

The clinical survey revealed evidence that the contraction in the peripheral anterior synechiae caused the corectopia. In the 40 cases in which gonioscopy was detailed enough for evaluation, the pupillary displacement was always in the direction of a peripheral anterior synechia. In some cases, the collarette was displaced locally toward the peripheral synechiae as an early sign of peripheral contraction. This clinical sign, which might be called the "distortion of the collarette" sign, can be an early clue to this disease process. Later the collarette was often drawn into the synechia and disappeared. In other cases, when the pupil was fairly central in the presence of extensive peripheral anterior synechiae, the location was explained by equal pull by peripheral anterior synechiae from many sides that dilated, but did not displace the pupil. This proved that corectopia does not cause the synechiae because synechiae occurred without marked corectopia.

We then searched for additional evidence that the ectopic membrane had contractile characteristics. A clinical study of eight patients with nodules showed that the region of nodule formation, and hence the region covered by an endothelial membrane, corresponded ex-

actly to the location of ectropion uveae and thus proved the contractility of this membrane.

The advancing edges of some active synechiae have been peculiarly yellow.[1] In the pathology specimens, redundant endothelial tissue was often visible at the leading edge of the synechiae, which might indicate the cause of the discoloration.

Chandler and Grant[1] also described a phenomenon they called "bridging" in this syndrome, found occasionally in an eye that had most of the angle obscured by forward peripheral anterior synechiae, but little glaucoma and little decrease in the tonographic facility of outflow. They speculated that open and functioning trabecular meshwork, with access to the anterior chamber, existed in tunnels behind these bridges. We encountered no such areas in our pathologic specimens, but the endothelial membrane overgrowth theory could account for this phenomenon if one visualized the endothelial membrane growing over the trabecular meshwork in one local area and then extending out onto the iris, finger-like and concentric to the pupil, and gradually drawing the iris to the cornea but leaving normal trabecular meshwork behind.

We then sought evidence that could connect the endothelial membrane theory to the development of iris atrophy. We noted, as had David D. Donaldson, M.D. (personal communication April 1, 1975), that two types of holes formed in this condition. One type, which we call a "melting" hole (Fig. 1, A), was oval and relatively small, and in the clinical survey was found to develop adjacent to and following the formation of heavy peripheral anterior synechiae. One can speculate that the adjacent atrophy of the iris was caused by local obstruction of the vasculature within the contracting synechia. Fluorescein iris angiograms revealed the occasional development of collateral vessels around the edges of these holes (Fig. 1, D), which confirmed a previous report,[29] and suggested that this mechanism may be correct.

The second type of hole, which is more common, and which we propose to call a "stretch" hole (Fig. 1, C), was large and bizarre. It occurred when the pupil was pulled far to one side, stretching the opposite iris and seemingly tearing it into large holes. In a parallel situation in normal eyes, however, when the pupil is drawn far to one side, either toward a cataract wound or an iridencleisis opening, holes are not torn in the opposite iris. The clinical survey revealed that peripheral anterior synechiae formed not only opposite the stretch holes, but also at the base of these holes and thus provided both traction and counter-traction. One might then argue that no iris, not even a normal one, could withstand this simultaneous pull from both sides without tearing into large stretch holes. In the spectrum of essential atrophy of the iris, there may be no underlying disease of the iris, and the atrophy may be secondary and caused solely by the endothelial membrane and its effect on normal iris tissue. As further support, in our pathologic survey, there was no evidence of a primary vascular disease in the iris,[3] and we therefore agree with those[8,28,30] who have reported none.

The results support a unifying theory. Endothelial degeneration led to corneal edema. Endothelial proliferation over open angle and followed by contraction caused synechiae, glaucoma, corectopia, and iris atrophy. Further extention onto the iris, with contraction, caused ectropion uveae and rarely, iris nodules (Fig. 3).

Discussion

This study is not the first to show that an ectopic endothelial membrane and its

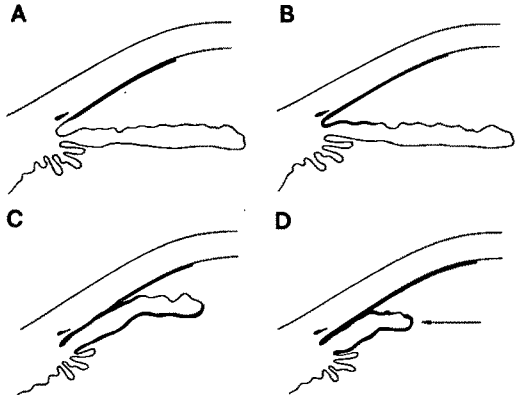


Fig. 3 (Campbell, Shields, and Smith). The proposed theory explaining essential iris atrophy: A, normal angle; B, downgrowth of endothelial membrane over open angle; C, contraction of membrane forming synechiae and causing corectopia and iris atrophy; D, further extention onto iris causing ectropion uveae, and, rarely, iris nodules.

contraction play an important role in essential iris atrophy.[6,8,15,20,31] However, this is the first study to present evidence that all of the bizarre pathologic findings can be explained by an endothelial membrane. These findings suggest, perhaps, that a new designation should be given to the syndrome. The name "primary proliferative endothelial degeneration" might be more appropriate. "Primary" is proposed to distinguish this proliferation from the secondary endothelial proliferations that occur after contact to the endothelium by iris, lens, or vitreous strands, or that follow inflammation, particularly luetic, or chronic angle recession. "Proliferative" is proposed because aberrant proliferation plays an overwhelmingly important role in this disease. "Degeneration" is proposed because it generally designates a deleterious process or change in the endothelium that is still not well understood. The term "metaplasia" could also be used.

There is a lack of visible breakdown products from the atrophic iris in the aqueous humor and in the trabecular meshwork because the stretch hole, which results from tearing of the iris with its contraction, but not loss, below the shrinking membrane.

The evidence indicating that the peculiar nodules in essential iris atrophy signal the presence and extent of an aberrant endothelial membrane on the iris gives clinicians the first clinical marker that this biomicroscopically invisible, new membrane is present within an eye. An associated flattening of the iris stroma with loss of normal architecture had been noted[14,15] and is another sign that the membrane is present. Ectropion uveae also heralds the presence of the membrane in the corresponding area in these eyes.

The finding that endothelial membrane overgrowth is common on the surface of the iris has practical surgical significance. In performing a peripheral iridectomy in a filtration procedure, the surgeon must take care to avoid inadvertently grasping this invisible membrane connected to the cornea, and then unknowingly removing it with connected corneal endothelium.

Evidence that the growth of an endothelial membrane probably causes peripheral anterior synechiae and glaucoma makes less practical the suggestion that a peripheral iridectomy[32] or removal of the iris[1,33] be performed in this condition to prevent further glaucoma.

The cause of essential iris atrophy is still unknown, but the evidence that diseased endothelium may play the primary role in the pathogenesis should stimulate further corneal studies. The scanning electron micrographs, which demonstrate aberrant endothelial cells over the angle and on the iris, show compact cells, which suggests that the membrane formation is not caused by expansion and sliding of existing corneal endothelial cells, but by actual multiplication of the cells. The initiating factor is unknown. Wheth-

er the cells initiate the process and grow over a normal trabecular meshwork, or whether an initial abnormality in the meshwork alters the natural boundary of the cells and permits the usurpation of adjacent territory, is unknown.

The degree of activity of the corneal endothelium may explain the clinical differences between Chandler's syndrome and progressive essential iris atrophy. In the former, there may be less activity, hence more corneal decompensation and less aberrant proliferation with less corectopia, glaucoma, and atrophy. In the latter, the endothelium may be less diseased and more active and may therefore better protect the cornea, but may proliferate more, and thus cause more severe corectopia, glaucoma, and iris atrophy.

Summary

We found that the spectrum of essential iris atrophy (progressive essential iris atrophy, Chandler's syndrome, and the Cogan-Reese syndrome) began as a corneal endothelial degeneration, which, with ectopic endothelial membrane overgrowth over an open angle, followed by contraction of this membrane and further growth onto the iris, accounted for all aspects of the syndrome. The contractile membrane caused the synechiae, the glaucoma, the corectopia, the ectropion uveae, the occasional iris nodules, and the iris atrophy. Thus we found this disease to be primarily of the cornea, and only secondarily of the iris. The results of this study led us to propose a new designation for this spectrum: primary proliferative endothelial degeneration.

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THE PREVALENCE OF HLA-B7 IN PRESUMED OCULAR HISTOPLASMOSIS IN PATIENTS WITH PERIPHERAL ATROPHIC SCARS

TRAVIS A. MEREDITH, M.D.
Milwaukee, Wisconsin
RONALD E. SMITH, M.D.
Los Angeles, California
RICHARD E. BRALEY, M.D., JOYCE A. WITKOWSKI, B.S.,
AND
SUSAN M. KOETHE, PH.D.
Milwaukee, Wisconsin

Presumed ocular histoplasmosis produces a distinctive clinical triad of changes in the ocular fundus: macular disciform scarring, peripapillary atrophy, and peripheral "punched-out" lesions. In a previous study, patients with a history of hemorrhagic macular or peripapillary lesions of presumed ocular histoplasmosis had an increased incidence of HLA-B7 (14 of 18).[1] A carefully performed epidemiologic study[2–5] in Walkersville, Maryland, identified patients with atrophic peripheral scars characteristic of presumed ocular histoplasmosis, but without a macular or peripapillary disciform process. Two independent examiners confirmed the clinical diagnosis without knowledge of skin test results; all of these patients were then found to have positive histoplasmin skin tests. We report herein the results of HLA typing of patients in the Walkersville study who were identified as having only peripheral atrophic spots.

From the Department of Ophthalmology (Drs. Meredith and Braley) and the Department of Pathology (Dr. Koethe and Miss Witkowski), the Medical College of Wisconsin and the Milwaukee County Medical Complex, Milwaukee, Wisconsin; and the Department of Ophthalmology (Dr. Smith), University of Southern California School of Medicine, Los Angeles, California.

Reprint requests to Travis A. Meredith, M.D., Department of Ophthalmology, 8700 W. Wisconsin Ave., Milwaukee, WI 53226.

MATERIAL AND METHODS

Twenty-one individuals were identified in the initial epidemiologic study[2–5] as having only peripheral atrophic scars with presumed ocular histoplasmosis. One patient subsequently died and another developed an active lesion of the posterior pole. Three patients moved away. Of the remaining 16 patients, 15 consented to participate in the current study and were typed for histocompatability antigens according to the National Institutes of Health lymphocyte microtoxicity technique.[6] The antigen frequency of the control population is based on the typing of 92 unrelated white individuals employed at the Milwaukee County Medical Complex. We correlated the results by using the chi-square test incorporating the Yeats correction factors described by Svejgaard for HLA and disease studies.[7]

RESULTS

Of the 15 patients studied, four (27%) were found to have HLA-B7. Compared with the frequency of HLA-B7 in the control population (20%), there is no statistically significant increase in this frequency ($P>.1$). Comparison of the frequency of HLA-B7 in the patients with peripheral lesions to that in patients with previous active posterior pole lesions (14

of 18) demonstrated a highly statistically significant difference between the frequency in the two groups ($.01 < P < .05$).

Discussion

Our data indicate no significant increase in HLA-B7 in patients with only peripheral atrophic spots in presumed ocular histoplasmosis, whereas patients with macular or peripapillary hemorrhagic lesions show a highly significant increase in the prevalence of this antigen. HLA typing reflects antigenic and genetic differences in individuals; thus our findings suggest that with ocular lesions caused by an infection with *Histoplasma capsulatum*, some patients have an inherent predisposition to develop active hemorrhagic posterior pole lesions based on these differences.

The study group for this report is unique because of its identification by examination of 842 patients in a small town in an endemic area with independent confirmation by two expert examiners.[2–5] As a group, the patients demonstrated no increase in the frequency of pulmonary calcification (2 of 16) over the general survey population (65 of 425), whereas 9 of 15 patients with macular disciform lesions have pulmonary changes on chest roentgenograms.[5] Mean induration of the histoplasmin skin tests in these patients was greater than in other skin test reactors in the survey population,[5] but was significantly less than a population of patients with macular scarring.[8] Patients with macular disciform lesions have also been shown to have an increased frequency of reaction to intermediate strength tuberculin skin test antigen (36.8%) compared to this group of patients with peripheral lesions who showed no increased frequency in skin test reactivity (15.1% vs 20% in controls).[8]

Immune hyperreactivity in patients with macular lesions of histoplasmosis was suggested by Weber and Schlaegel[9] on the basis of their findings that patients with macular disease reacted to more skin tests than other uveitis patients. Ganley[10] supported this interpretation with findings in lymphocyte transformation studies that lymphocytes from patients with disciform lesions showed a greater spontaneous blast transformation than did lymphocytes from this group of patients with only peripheral lesions.

The interpretation of the association of different diseases with specific HLA types is complex. Associations with certain histocompatibility antigens have been shown in four broad categories of disease: (1) leukemias and lymphomas, (2) cancer other than lymphoma, (3) immunopathic disease, including those with an autoimmune component, and (4) certain infections.[11] Possible mechanisms of these associations that might explain the differences between the two groups of patients in our data include molecular mimicry, linkage of B loci genes to immune response genes, alteration of cytotoxicity of T cells, alterations in genes affecting structural components of complement, or linkage of B loci genes to other genes.[12] Molecular mimicry means that HLA surface antigens of some patients are similar to invading organisms so that there is an altered host response. Linkage disequilibrium between HLA-B loci and genes in the D locus region, presumably related to immune response genes, has been shown for several diseases. In Sjögren's syndrome, for example, association of the disease was made with HLA-B8, but subsequent studies demonstrated a stronger association with HLA-DW3, so that the HLA-B8 locus was only secondarily involved through linkage disequilibrium.[13] Linkage disequilibrium between B loci and genes not involved with the immune response may also exist. B loci may also secondarily reflect genes that control the structure of complement,

and complement deficiencies seem to predispose to certain types of autoimmune disease.

Finally, B loci are involved in the specificity of cytotoxic T cells, making it theoretically possible that certain HLA-B loci antigens could be linked with more or less effective T-cell-mediated cytotoxic responses to invading organisms.

Woods and Wahlen[14] originally proposed that the formation of disciform scars in the posterior pole might result from a local hypersensitivity reaction. Lymphocytes have been identified in the base of disciform scars[15–17] and in peripheral scars as well, and they may play an active role in an immunologically mediated "reactivation."[18] Although a specific HLA type might identify individuals predisposed to a late reactivation through some immunologically mediated mechanism, the effect of the initial infection might be different in these individuals, thereby also accounting for the increase in pulmonary scarring observed in patients with macular disease. Because subretinal neovascularization occurs most often at the site of established atrophic scars in the posterior pole,[19–21] more severe initial damage might predispose patients to late passive decompensation at the site of these lesions more commonly.

The strong difference in incidence of HLA-B7 in the populations of patients with peripheral disease and with macular disease suggests that the B7 antigen may have predictive value. In patients with only atrophic macular scars, the presence of HLA-B7 may identify patients at greater risk for development of an active posterior pole lesion.

SUMMARY

Patients identified in the Walkersville, Maryland, epidemiologic study of presumed ocular histoplasmosis as having only peripheral atrophic scars showed no increase in frequency of HLA-B7 over a control population. Because this antigen is increased in patients with a history of active macular or peripapillary lesions, these findings indicate an inherent predisposition in some patients to develop posterior pole lesions after an ocular infection with *Histoplasma capsulatum*. The precise mechanisms by which the histocompatibility complex participates in the pathogenesis of these lesions is unknown, but our data are compatible with previous suggestions that alterations in the immune response of these individuals are in some way important in the development of disciform scarring in the posterior pole.

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OPHTHALMIC MINIATURE

Notes and queries

Subscribers are requested to be as minute in the description of cases, on which they consult us, as possible. We do not make any charge for our answers, but will always take the privilege to use the histories of interesting cases as contributions to this Journal. Contributors will please send their manuscripts some weeks before the publication of each number. Writers on Ophthalmic Surgery in all parts of America and Europe are most cordially invited to become contributors or correspondents. European Oculists will greatly facilitate our labors by sending us copies of their publications.

We have found it necessary, on account of the less frequent appearance of this Journal, to answer by letter all inquiries, as speedily as possible. We shall, henceforward, take the same course, and do away with "answers to correspondents" in this department.

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CYTOMEGALOVIRUS IN JUVENILE IRIDOCYCLITIS

WILLIAM M. HART, JR., M.D., CHARLES A. REED, A.B.,
HOWARD L. FREEDMAN, M.D., AND RONALD M. BURDE, M.D.
St. Louis, Missouri

Cytomegalic inclusion disease is a clinical syndrome with protean manifestations in newborn infants.[1-4] The etiologic agent, cytomegalovirus, a DNA virus that belongs to the herpesvirus family, is most frequently involved ocularly in infants as a chorioretinitis associated with prematurity, fever, hepatosplenomegaly, jaundice, anemia, pneumonia, intracerebral calcifications, and commonly, death. Active infection has been identified in adults whose immunocompetence has been compromised.[5-8] We report a case of cytomegalovirus that was cultured from the eye of an otherwise healthy child with juvenile iridocyclitis.

CASE REPORT

At age 3 years and 9 months, a boy was referred to us for examination of a recent onset of leukocoria of the right eye. He had been the product of a normal pregnancy, labor, and delivery and had weighed 3,892 g at birth. He had had a normal growth and development pattern and had been asymptomatic before discovery of the leukocoria. Visual acuity was R.E.: light perception; L.E.: 6/20 (20/400). There was an early band keratopathy in both eyes, and cells and aqueous flare were visible in both anterior chambers. There were no keratitic precipitates. The pupils were 3 mm in diameter and fixed to light, and both eyes had advanced pupillary seclusion. The right eye had a mature cataract, and the lens of the left had advanced cortical opacities. Intraocular pressure was low by tactile estimation. Ultrasonographic examination with a contact B-scan instrument showed normal appearing retrolenticular structures. During hospital admission the following studies were found to be normal or negative: complete blood cell count, urinalysis, chest x-ray, x-rays of skull and orbits, computed tomography scan (EMI), erythrocyte sedimentation rate, VDRL, fluorescent treponemal antibody test, antinuclear antibodies, latex fixation, agglutinating and complement-fixing antibodies for histoplasmosis and toxoplasmosis, and skin testing with purified protein derivative (intermediate strength) and mumps antigen. The patient remained afebrile, and there were no other abnormal findings on physical examination.

After three days of 20 mg/day of orally administered prednisone, the patient underwent uneventful aspiration of the cataract in the right eye. The aspirated lens material was submitted for viral culture. A periocular injection of 2 mg of dexamethasone was given, the oral prednisone was discontinued, and topically applied mydriatics and corticosteroids were used bilaterally. Four weeks later, examination under anesthesia revealed an anterior vitritis in the operated eye with an early iridocyclitic membrane. An opening was made in the membrane with a Sato needle knife, and the patient again began receiving 20 mg/day of prednisone. Both eyes remained hypotonic (intraocular pressure by applanation tonometry was less than 8 mm Hg), and the cataract in the left eye was mature. One week later, the left lens was aspirated, and periocular injections of 0.5 ml of methylprednisolone acetate (80 mg/kg of body weight) were given bilaterally. Postoperatively, the inflammatory process abated in both eyes. Six weeks following the second cataract aspiration, a clear view was obtained of a normal fundus bilaterally. The patient was monitored on a slowly tapered course of oral prednisone. Eight months after the original visit, visual acuity was 6/6 (20/20) in both eyes with aphakic spectacle correction.

Five months after the first cataract operation, cell cultures were positive for cytomegalovirus. Rhesus monkey kidney and human epithelial cell cultures were negative for mumps, rubella, enterocytopathogenic human orphan virus, coxsackie, polio, herpes, and adenoviruses. On a fibroblast cell culture (Wistar Institute 38) the first passage was toxic (all cells immediately destroyed). On the second passage a cytopathologic effect was noted on the 21st day. Serial passages were performed, and on the sixth passage, a 90% cytopathologic effect was observed by the 21st day. This culture tube was stained and showed typical intranuclear inclusion bodies. A seventh passage was made using cells grown out on a microscope slide cover slip (Figs. 1 to 3). A urine specimen from the patient's mother failed to reveal cytomegalovirus, and complement fixing antibodies to cytomegalovirus were less than 1:8 on blood samples from both patient and mother. Neutralizing antibodies in the patient's serum were measured as the serial dilution capable of producing 50% inhibition of cytopathologic effect of the virus grown in the same cell culture. The end point was taken at the time control cultures (uninhibited) showed 90% cytopathologic effect. By this method, neutralizing

From the Departments of Ophthalmology (Drs. Hart, Freedman, and Burde) and Pediatrics (Mr. Reed), Washington University School of Medicine, St. Louis, Missouri.

Reprint requests to William M. Hart, Jr., M.D., Department of Ophthalmology, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110.

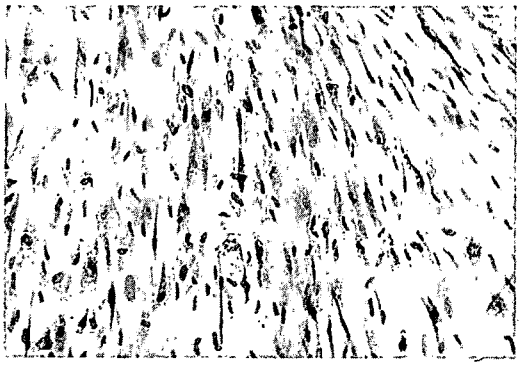


Fig. 1 (Hart and associates). Control (uninoculated) culture of Wistar Institute 38 fibroblasts (Giemsa, × 100).

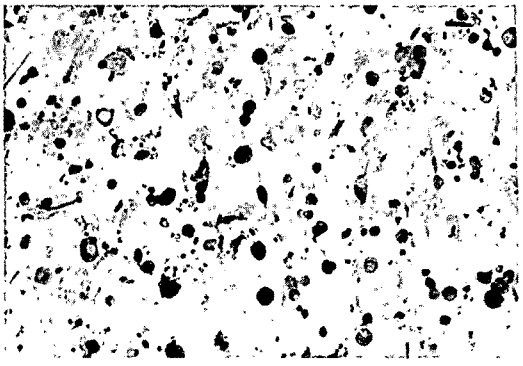


Fig. 3 (Hart and associates). Detail of intranuclear inclusion bodies in infected cell culture (Giemsa, × 250).

antibodies were present at a 1:4 dilution in the acute phase (serum collected at the time of surgery), and had fallen to 1:1 in the convalescent phase (eight months after surgery).

Discussion

Whereas clinical disease caused by congenital cytomegalovirus infection is uncommon, immunologic evidence has shown that clinically inapparent involvement of cytomegalovirus is common in both congenitally and natally acquired infections.[9,10] In perinatally acquired disease (identified serologically), congenital ocular pathology has been associated with excessive in utero viral production, whereas the congenital syndrome (including chorioretinitis) has failed to develop later if no indication of the disease is present at birth.[11,12] However, an epidemiologic association between serologic evidence of viral infection and less severe ocular disorders (strabismus and nystagmus) has been reported.[13] Recent evidence suggests that cytomegalovirus infection is transmitted venereally among adults,[14] whereas natally acquired infection is probably related to maternal cervical and urinary tract shedding of the virus.[15] The isolation of the virus from the eye of a child with an apparently acquired disease has several implications. Although the presence of the virus in this instance may be simply fortuitous and not etiologic, ocular infection by the related herpesvirus is known to produce a chronic recurrent inflammatory disease thought to be an immunologic response to the presence of virus or combined virus-host antigen.

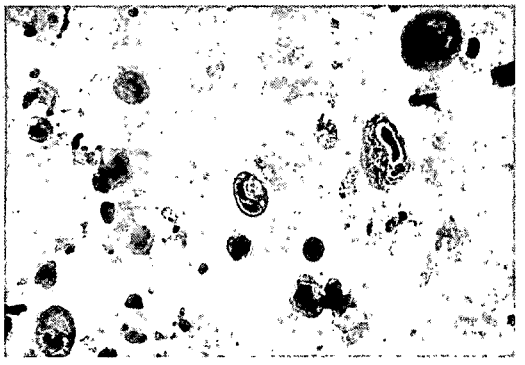


Fig. 2 (Hart and associates). Cytopathologic effect in cell culture inoculated with serial passage of virus cultured from patient's aspirated lens material (Giemsa, × 100).

Juvenile iridocyclitis is a chronic disorder that is suppressed by the use of corticosteroids. The side effects that this class of drugs produces in maturing children are legion.[16] If indeed viral agents can be isolated from the eyes of patients with juvenile iridocyclitis with regularity, there would be a rationale for initiating treatment systemically with specific anti-

viral agents (that is, vidarabine).[17] The use of such specific agents, if effective in the early course of the disease, could possibly prevent the development of known sequelae of chronic iridocyclitis such as band keratopathy, secondary glaucoma, and cataract formation. Furthermore, effectiveness of such agents would obviate the need for prolonged use of corticosteroids.

Summary

We cultured cytomegalovirus from lens material aspirated from the eye of a 4-year-old boy who had a severe bilateral iridocyclitis and secondary cataracts. There were neither systemic manifestations of congenital disease nor chorioretinitis.

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EFFECTS OF PANRETINAL PHOTOCOAGULATION ON RUBEOSIS IRIDIS, ANGLE NEOVASCULARIZATION, AND NEOVASCULAR GLAUCOMA

MARTIN WAND, M.D., DAVID K. DUEKER, M.D., LLOYD M. AIELLO, M.D., AND W. MORTON GRANT, M.D.

Boston, Massachusetts

One of the major ophthalmic complications of diabetes mellitus is neovascular glaucoma. Until recently, there was little that could be done to delay the relentless progression of this complication. Several recent publications have suggested that panretinal photocoagulation could cause the regression of rubeosis iridis and angle neovascularization. Unfortunately, these studies have involved only small numbers of patients over short time periods. Between 1967 and 1971 at the Beetham Eye Unit of the Joslin Clinic, patients with diabetic proliferative retinopathy received ruby laser panretinal photocoagulation in one eye only, the opposite eye serving as control. This is the longest ongoing controlled study of this nature, and, as such, offers a unique population for further investigation. We studied this population to determine the late effects of panretinal photocoagulation on development of rubeosis iridis, angle neovascularization, and neovascular glaucoma. This report is based on the results of our study.

SUBJECTS AND METHODS

Between 1967 and 1971, 184 patients received panretinal photocoagulation in one eye only and were eligible for this study, as they had been observed for a minimum of five years. These patients were originally selected for treatment of their proliferative retinopathy in one eye only, with the fellow eye serving as the untreated control eye. In general, the eye with the more advanced retinopathy was selected for treatment. During this time, 43 (23.4%) patients died and 22 patients (11.9%) were lost to follow-up; but adequate data were available to demonstrate that the patients lost to follow-up had not biased the results either in favor or against the beneficial effects of laser treatment. Of the remaining 119 patients, 93 patients returned for reevaluation. Including the 22 patients who were initially lost to follow-up, a total of 48 patients from the original panretinal photocoagulation group of 184 patients were not included in this study.

The American Optical pulsed ruby laser photocoagulator (6943 angstroms) with a monocular indirect ophthalmoscope viewing system was used with an aperture of 2.5 degrees to produce chorioretinal lesions 0.75 mm in diameter. The power setting was calibrated for individual patients in an attempt to produce lesions of grade 1 or 2 intensity.[1] Anesthesia was not required for any patient. At each session 200 to 300 applications were applied to all areas of the posterior pole, sparing the disk, macula, and maculopapilla bundle as described in a previous report.[2] The average total application per eye was 636 (range 283 to 1,140) during three treatment sessions approximately one month apart.

The examination procedure for this study consisted of measuring the best

From the Beetham Eye Unit, Joslin Clinic (Drs. Wand and Aiello), the Glaucoma Consultation Service, Massachusetts Eye and Ear Infirmary, and the Howe Laboratory of Ophthalmology, Harvard Medical School (Drs. Wand, Dueker, and Grant), Boston, Massachusetts. This study was supported by United States Public Health Service Research grants 1-R01-EY00643, 5-R01-EY00002, and EY01750-01 from the National Eye Institute. Dr. Wand was a Heed Fellow (1975-1976).

Reprint requests to Martin Wand, M.D., 100 Retreat Ave., Hartford, CT 06106.

corrected visual acuity and the applanation pressure of each eye, and performing careful slit lamp microscopy of the iris and angle. The Haag-Streit slit lamp with ×10 ocular pieces and the Goldmann gonioscopy lens were used. These examinations were always performed by two of us (M.W. and D.D.) independently, with neither examiner knowing which eye of the patient had received the panretinal photocoagulation. Any rubeosis iridis and angle neovascularization were noted independently on a special drawing chart devised by one of us (D.D., Fig. 1). After the examination was completed by each examiner, the findings were compared, and the eyes were examined again together if any discrepancies were found. Only then was the clinical chart of the patient examined to determine which eye had received the panretinal photocoagulation.

RESULTS

Among the 93 patients were 42 women and 51 men, with an average age of 47.6 years (22 to 76 years range). The right eye was treated in 39 cases and the left eye in 54 cases. The average follow-up time was 7.1 years (range, five to nine years).

In 14 patients, the treated eye did not develop rubeosis iridis, but the contralateral untreated eye did. In three patients, the treated eye developed rubeosis iridis and the contralateral untreated eye did not develop rubeosis iridis (Table). This relationship is statistically significant at $P < .025$, by McNemar's test for correlated proportions.[3] Twenty-three of the untreated eyes compared to 12 of the treated eyes developed rubeosis iridis, meaning that rubeosis developed bilaterally in nine patients.

In seven patients, the treated eye did not develop angle neovascularization, but the contralateral untreated eye did develop angle neovascularization. In no patient

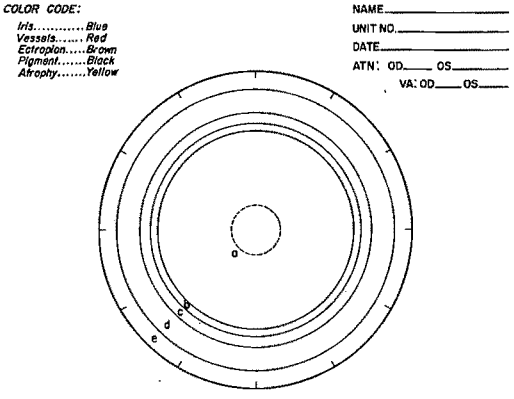


Fig. 1 (Wand, and associates). Chart for recording rubeosis iridis and angle neovascularization. a designates pupil; b, ciliary body band; c, scleral spur; d, filtration portion of trabecular meshwork; e, nonfiltration portion of trabecular meshwork.

TABLE

EFFECT OF PANRETINAL PHOTOCOAGULATION ON THE INCIDENCE OF RUBEOSIS IRIDIS, ANGLE NEOVASCULARIZATION AND NEOVASCULAR GLAUCOMA

Status of Eyes	No. of Patients
Rubeosis Iridis (P<.025)	
Present in both treated and untreated eyes	9
Absent in both treated and untreated eyes	67
Present in untreated eyes, absent in treated eyes	14
Present in treated eyes, absent in untreated eyes	3
Angle Neovascularization (P<.025)	
Present in both treated and untreated eyes	3
Absent in both treated and untreated eyes	83
Present in untreated eyes, absent in treated eyes	7
Present in treated eyes, absent in untreated eyes	0
Neovascular Glaucoma	
Present in both treated and untreated eyes	1
Absent in both treated and untreated eyes	88
Present in untreated eyes, absent in treated eyes	4
Present in treated eyes, absent in untreated eyes	0

did angle neovascularization develop in the treated eye and not in the contralateral untreated eye (Table). This relationship is statistically significant at $P < .025$.[3] Ten of the untreated eyes developed angle neovascularization as compared to three of the treated eyes.

In four patients, the treated eye did not develop neovascular glaucoma but the contralateral untreated eye did develop neovascular glaucoma. In one patient both the treated eye and the contralateral untreated eye developed neovascular glaucoma (Table). This, however, is not statistically significant.

From our observations in the course of this study, and in related work, we have been able to obtain a good concept of the natural developmental course and progression of anterior segment neovascularization. Diabetic rubeosis iridis first begins at the pupillary margin with dilated tufts of preexisting capillaries and fine new capillary formation (Fig. 2). This may be easily missed if not looked for specifically under high magnification with a slit lamp. At this stage, these dilated capillary tufts are sensitive to pressure, and excessive pressure with the Goldmann lens can cause them to blanch, disappear from view, and be missed on examination. However, even before this clinically visible stage, the iris vessels, especially around the pupillary margin, leak fluorescein during iris angiography.[4] We have not seen new vessel formation elsewhere on the iris without seeing new vessels on the pupillary margin. As the rubeosis progresses, radial vessels tend to join vessels in the collarette, seemingly to distend this previously present but nonfunctional vessel.

New vessels then branch off radially from the collarette to the far periphery. Of great clinical significance, and contrary to what has been thought,[5] we have not seen a case of angle neovascularization (15 cases) or neovascular glaucoma (five cases) without some pupillary rubeosis iridis being present as well. This rubeosis may be subtle, but, if looked for carefully, cannot be missed. The neovascularization appears to progress in an orderly fashion, starting at the pupillary margin and proceeding radially to the angle. The new vessels in the angle can sometimes be seen coming off the circumferential ciliary body artery, then crossing over the ciliary body band and scleral spur, and on reaching the trabecular meshwork, arborizing over it.

Discussion

In the United States, diabetes mellitus is now the most common cause of newly reported cases of blindness in people aged 40 to 60 years.[6] Although neovascular glaucoma accounts for only a small proportion of these new cases of blindness, neovascular glaucoma has always been especially dreaded because there has been no adequate prophylaxis or treatment for it.[7] Within the past few years, several avenues of research have suggested the possibility of treating this complication. Aiello and Briones[1] and Beetham and associates[8] showed in 1968 that ruby laser panretinal photocoagulation improved diabetic neovascular retinopathy. Their findings were confirmed in a much larger controlled study using the argon laser or xenon arc for the panretinal photocoagulation.[9] Whatever the cause of this improvement, it appears that panretinal photocoagulation reduced or eliminated the stimulus for new vessel formation in the posterior pole.

The possibility that the cause of anterior segment neovascularization may be the same as for the posterior segment neovascularization is suggested by the fact that, while the incidence of rubeosis iridis in unselected diabetic populations has been reported to be from 1%[10] to 17%,[11] the incidence of rubeosis iridis in patients with proliferative retinopathy has been

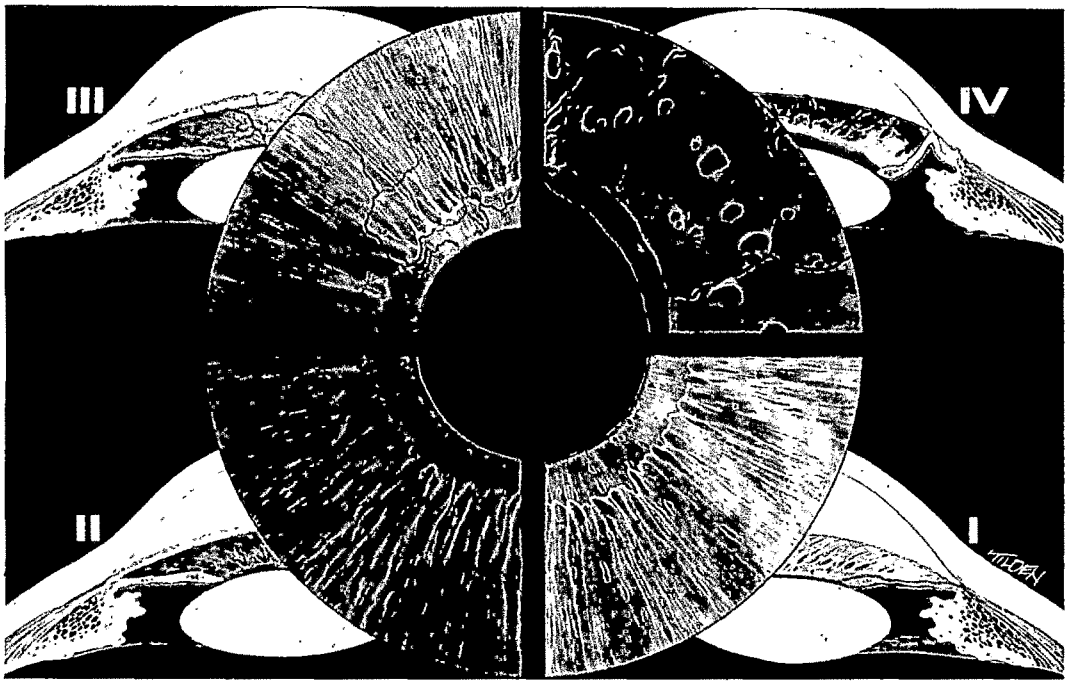


Fig. 2. (Wand and associates). I. Early rubeosis iridis. Dilated capillary tufts are present only at the pupillary margin; the angle is not involved. II. Moderate rubeosis iridis. New vessels extend radially towards the angle, sometimes joining a dilated vessel at the collarette; the angle is still not involved. III. Advanced rubeosis iridis with angle neovascularization. New vessels reach the angle and join the circumferential ciliary body artery; new vessels come off this artery, cross over the scleral spur onto the trabecular meshwork where arborization occurs. One area of synechial closure is shown. Pressure can increase at this stage. IV. More advanced neovascular glaucoma. The angle is completely closed; the iris is pulled up over the whole trabecular meshwork and hides all angle structures posterior to Schwalbe's line; the pupil shows ectropion and distortion. A "burned-out" stage can occur later; then there may appear to be little rubeosis iridis, and only an occasional vessel may be seen approaching a completely closed angle.

reported to be from 33%[12] to 64%.[13] The regular presence of diabetic retinal neovascular changes in patients with rubeosis iridis was reported as early as 1939.[14] This highly significant correlation suggests that a common agent causes the new vessel formation in the retina and on the iris.

Krill, Archer, and Newell[15] first demonstrated that photocoagulation of the retina could cause disappearance of the new vessels on the surface of the iris. This was subsequently confirmed in a case report,[16] in a retrospective study of 11 patients,[17] and in a prospective study of ten patients.[18] Inasmuch as panretinal photocoagulation offered the possibility of an effective prophylaxis and treatment for neovascular glaucoma, a larger study with a longer follow-up seemed desirable.

The original group of patients who participated in the ruby laser panretinal photocoagulation study of Aiello and coworkers[2] presented the ideal patient group for our study. They received no other forms of therapy known to affect the eyes, and they had been observed at least five years. Although gonioscopy was not performed before the photocoagulation treatment, all patients did have a thorough slit-lamp and fundus examination with applanation pressure measurements.

Results of our subsequent examinations showed a statistically significant difference between eyes that received panretinal photocoagulation and eyes that did not in regard to the subsequent development of rubeosis iridis and angle neovascularization. This treatment also seems to have a protective or preventive effect on the development of neovascular glaucoma; although the difference between the treated and untreated eyes was not statistically significant, the findings suggest the treatment also exerts a protective effect against this complication. The finding that, in four patients, the treated eye did not develop neovascular glaucoma and the fellow untreated eye did is especially suggestive to us because in untreated patients, when diabetic neovascular glaucoma develops in one eye, it almost always develops in the fellow eye.[5,19]

The many ocular problems that may cause rubeosis iridis are already known.[20] In contrast to François,[21] others believe that neovascularization of the iris and angle resulting from diabetes and other causes is indistinguishable clinically and histologically.[7,22,23] The cause of this new vessel formation is still not established, but experimental work suggests an "angiogenesis factor" may be a mediating factor for neovascularization.[24,25] In a preliminary study, an angiogenesis factor has been found through a bioassay technique in the aqueous of three of five patients with neovascular glaucoma (personal communications from A. R. Bellows, D. Tapper, R. Langer, and J. Folkman, April 29, 1976).

The common denominator in various ocular conditions that manifest neovascularization appears to be relative anoxia; and it follows that some factor that stimulates new vessel formation may be produced by the anoxic retinal. This factor would logically have the most profound effect on nearby structures, and then, as it diffused through the pupil and out the angle, would have less effect on more distant structures. We have found decreasing incidence of neovascularization from the retina to the iris to the angle.

If an anoxic retina produces an angiogenic factor, retinal ablation may prevent the production of this factor by destroying the anoxic retina. Occasionally, rubeosis iridis and neovascular glaucoma spontaneously stop progressing and actually regress.[7,19,26] This has been attributed to retinal destruction from progression of the initial retinal disorder.[26] Panretinal photocoagulation presumably contributes to destruction of the anoxic retinas.

That panretinal photocoagulation did not completely prevent the development

of rubeosis iridis, angle neovascularization, and neovascular glaucoma may have several explanations. The 12 treated eyes that developed rubeosis iridis had an average of 481 spots of treatment (range, 177 to 803) compared to an average of 651 spots of treatment for the eyes that did not develop rubeosis iridis. The eyes that received fewer spots of treatment may not have had adequate destruction of the anoxic retina. Another factor to be considered is not just the quantitative aspect of the panretinal photocoagulation, but the qualitative aspect. An eye with more nuclear sclerosis or vitreous opacities, or both, receives less effective therapy than an eye with a clear lens and media, regardless of the total number of spots received. We are not able retrospectively to evaluate the clarity of the optical media in this study. We suspect the effect of panretinal photocoagulation on anterior segment neovascularization would be even more statistically significant if adequate numbers of full strength photocoagulation spots were delivered to all areas of anoxic retina. However, this will be difficult to establish because it is unlikely that such a large controlled population study with one eye treated and one eye untreated can be carried out again to repeat our evaluations; additionally, the convincing beneficial results of panretinal photocoagulation on proliferative diabetic retinopathy have now established a precedent to treat all such eyes.[7]

We believe the treatment of neovascular glaucoma may be entering a new phase. This study shows that panretinal photocoagulation in eyes with proliferative retinopathy seems to decrease the incidence of rubeosis iridis, angle neovascularization, and probably neovascular glaucoma. Although the study does not show that panretinal photocoagulation actually improves the prognosis of such eyes, we believe, based on a small number of cases we have treated and followed, that panretinal photocoagulation delays or aborts the progression of rubeosis iridis to neovascular glaucoma.

SUMMARY

Ninety-three patients received ruby laser panretinal photocoagulation in one eye for diabetic retinopathy and we examined them at an average time of 7.1 years later. In 14 patients, the untreated eye developed rubeosis iridis and the contralateral treated eye did not. In seven patients, the untreated eye developed angle neovascularization and the contralateral eye did not. The untreated eye developed neovascular glaucoma and the contralateral treated eye did not in four patients.

Our findings suggest that eyes with proliferative retinopathy that receive panretinal photocoagulation are less likely to develop rubeosis iridis, angle neovascularization, and probably neovascular glaucoma, than those eyes not receiving panretinal photocoagulation.

ACKNOWLEDGMENT

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LONG-TERM TREATMENT OF GLAUCOMA WITH SYSTEMIC PROPRANOLOL

ARNE ÖHRSTRÖM, M.D.
Köping, Sweden
AND
MAURIZIO PANDOLFI, M.D.
Malmö, Sweden

Propranolol, an adrenergic $beta_1$ and $beta_2$ blocker without intrinsic sympathomimetic activity, has been used in the treatment of ocular hypertension and glaucoma.[1-12] Propranolol reduces the intraocular pressure (IOP) when given topically or systemically.

Besides propranolol, other beta blockers decrease IOP, namely practolol, a $beta_1$-blocker with intrinsic sympathomimetic activity[11,13]; pindolol, a $beta_1$-blocker with intrinsic activity[14]; atenolol, a $beta_1$-blocker without intrinsic activity[15-17]; oxprenolol, a $beta_1$- and a $beta_2$-blocker with an effect similar to that of propranolol, but with less depressant effect on the heart[18]; and timolol, a pure $beta_1$- and $beta_2$-blocker.[19]

We describe herein the treatment of glaucoma with systemic administered propranolol for a maximum period of 3½ years.

SUBJECTS AND METHODS

We studied 19 patients, none of whom had diseases such as cardiac incompensation or asthma contraindicating the use of propranolol. Sixteen patients had open-angle glaucoma in one (seven patients) or both eyes (nine patients) with visual field defects, glaucomatous cupping of the optic disk, and IOP exceeding 24 mm Hg. One patient had secondary glaucoma caused by Fuchs' heterochromic iritis with IOP fluctuating between 30 and 60 mm Hg. The remaining two patients had ocular hypertension bilaterally with IOP values exceeding 30 mm Hg. In the patients with glaucoma, conventional medical therapy had been tried without success, and their IOP was still considered too high. They were receiving maximal therapy. Oral propranolol was added to the treatment in doses of 20 to 40 mg three to four times a day. Treatment with propranolol was continued as long as the IOP did not exceed 22 mm Hg or no worsening of visual field defects or of optic disk cupping was demonstrable.

Four to six times a year, a trained assistant unaware of the trial examined the perimetry and IOP of the patients with the Goldmann applanation tonometer. The cupping of the optic disk was evaluated by estimating the cup:disk ratio.

The IOP reduction was calculated from the baseline IOP recorded immediately before the beginning of treatment with propranolol and the mean value of the three highest IOP values recorded during treatment.

The systemic blood pressure in supine position was measured after ten minutes' rest. The blood pressure the day before the treatment was started was compared with the mean of the three lowest values of blood pressure during treatment.

RESULTS

Therapeutic effect—GROUP 1: In seven patients (Nos. 1 to 7) the IOP was kept

From the Department of Ophthalmology, Hospital of Köping (Dr. Öhrström); the Department of Ophthalmology, Hospital of Malmö the University of Lund (Dr. Pandolfi), Sweden. This study was supported by grants from Thorsten and Elsa Segerfalk's Fund for Medical Research (Dr. Pandolfi).

Reprint requests to Arne Öhrström, M. D., Department of Ophthalmology, Hospital of Köping, S-731 01 Köping, Sweden.

below 23 mm Hg and visual field defects did not worsen. Mean IOP reduction was 13 mm Hg, and mean follow-up was 30 months. Treatment with propranolol is still being given.

GROUP 2: In four patients (Nos. 8 to 11) the IOP was kept below 23 mm Hg for a mean duration of five months, and visual field defects did not worsen. However, because of side effects, propranolol had to be withdrawn. Mean IOP reduction was 6 mm Hg.

GROUP 3: In three patients (Nos. 12 to 14) the IOP was kept below 23 mm Hg for two, 12, and 42 months, respectively, after which the trial was interrupted because of increasing IOP. After propranolol had been used for about one year, it was tentatively withdrawn from patient No. 14. The IOP rose immediately to pretreatment values, and therapy with propranolol was resumed. Mean IOP reduction was 18 mm Hg, and mean follow-up was 19 months.

GROUP 4: In five patients (Nos. 15 to 19) the visual field defects worsened during treatment with propranolol. Of these patients, in three (Nos. 15, 18, and 19) the visual field defects were worsening before the treatment with propranolol. Remarkably enough, the visual field defect continued to worsen in one eye (patient No. 16), on which a fistulizing operation was later successfully performed. The treatment with propranolol was continued to control the pressure in the fellow eye, which showed no worsening. The remaining patient (No. 17) showed increasing scotoma after 14 months of treatment in spite of IOP below 23 mm g. Mean follow-up was 20 months, and mean IOP reduction was 9 mm Hg (Table 1).

Effect on blood pressure—In four patients, no reliable records of the blood pressure before treatment were available. In three patients, no change in blood pressure was noted, whereas treatment was followed by a decrease in seven patients and an increase in five (Table 2).

Side effects—Nine patients complained of fatigue, insomnia, and chills. Some patients were disturbed by bradycardia. In four patients, these symptoms were so severe that the drug was withdrawn. The other five patients described the symptoms as moderate and less troublesome than those caused by acetazolamide.

DISCUSSION

The findings in a selected group of patients with pathological IOP not responding to the conventional therapy showed that addition of propranolol reduced the IOP to acceptable levels ($\leq$22 mm Hg) for periods of up to 3.5 years.

The maximum IOP decrease varied between 6 and 30 mm Hg, and, as expected,[2,12] it was generally more pronounced when the original IOP was high.

After having remained unchanged for a period, the visual fields continued to deteriorate in five patients during treatment. However, three of them had almost total cupping of the optic disk and large visual field defects, namely, signs of a poor prognosis. The deterioration apparently could not be attributed to a reduction in blood pressure by propranolol because blood pressure was unchanged in four patients and decreased in only one. (The remaining six patients with reduced blood pressure did not show any impairment of the visual field.)

In the doses used, propranolol usually had only a moderate effect, if any, on the blood pressure, except in one case (No. 6) in which it changed from 190/100 to 130/90 and propranolol had to be withdrawn because of the effects of hypotension and bradycardia. The cause of an occasional increase in blood pressure noted in some cases is unknown.[20]

Administration of propranolol in the doses used in this study, namely, 20 to 40 mg three to four times a day, may decrease systemic blood pressure which, theoretically, could decrease the perfusion pressure in the optic nerve head.

TABLE 1

EFFECTS OF PROPRANOLOL

	Patient Code No.	Time of Treatment (mos)	IOP Reduction (mm Hg)	Progress of Visual Field Defects	Side Effects	Systemic Blood Pressure (mm Hg)	Diagnosis
Group 1							
Satisfactory	1	32	20	0	0	170/80-155/90	Open-angle glaucoma both eyes
control of IOP	2	41	10	0	0	200/105-180/100	Open-angle glaucoma RE
(IOP≤22 mm Hg)	3	23	6	0	+		Open-angle glaucoma both eyes
	4	43	6	0	0		Open-angle glaucoma RE
	5	29	15	0	0	210/90-106/85	Ocular hypertension both eyes
	6	23	20	0	+	125/75-110/65	Open-angle glaucoma both eyes
	7	19	15	0	+	150/80-130/70	Open-angle glaucoma RE
		Mean: 30 mos	Mean: 13 mm Hg				
Group 2							
Satisfactory	8	11	6	0	+	170/80-180/90	Open-angle glaucoma both eyes
control of IOP,	9	1	6	0	+	125/70-125/70	Open-angle glaucoma RE
but side effects	10	6	6	0	+		Open-angle glaucoma RE
	11	2	6	0	+	190/100-130/90	Open-angle glaucoma LE
		Mean: 5 mos	Mean: 6 mm Hg				
Group 3							
Satisfactory	12	12	15	0	0	120/75-140/75	Open-angle glaucoma RE
control of IOP, but withdrawal of drug	13	2	30	0	0	155/80-160/80	Glaucoma secondary to Fuchs' heterochromia RE
because of increasing IOP	14	42	10	0	0		Ocular hypertension both eyes
		Mean: 19 mos	Mean: 18 mm Hg				
Group 4							
Drug withdrawn	15	31	10	+	+	170/100-140/80	Open-angle glaucoma both eyes
because of in-	16	31	10	+ and −	0	120/60-140/65	Open-angle glaucoma both eyes
creasing	17	14	6	+	+	160/85-160/85	Open-angle glaucoma both eyes
visual field	18	20	12	+	0	150/85-195/95	Open-angle glaucoma both eyes
defects	19	6	8	+	0	140/90-140/90	Open-angle glaucoma both eyes
		Mean: 20 mos	Mean: 9 mm Hg				

TABLE 2

EFFECT OF PROPRANOLOL ON BLOOD PRESSURE

	Patient Code No.	Blood Pressure (mm Hg)		Blood Pressure Changes During Treatment (mm Hg)		Remarks
		Before Treatment	After Treatment	Systolic	Diastolic	
Increase in blood pressure	8	170/80	180/90	+10	+10	Propranolol withdrawn because of side effects (insomnia, asthenia)
	12	120/75	140/75	+20	–	
	13	155/80	160/80	+ 5	–	
	16	120/60	140/65	+20	+ 5	Visual field defect worsening
	18	150/85	195/95	+45	+10	Visual field defect worsening
Decrease in blood pressure	1	170/80	155/90	−15	+10	
	2	200/105	180/100	−20	− 5	
	5	210/90	160/85	−50	− 5	
	6	125/75	110/65	−15	−10	Insomnia, side effects
	7	150/80	130/70	−20	−10	Chills, side effects
	11	190/100	130/90	−60	−10	Propranolol withdrawn because of side effects (asthenia, bradycardia)
	15	170/100	140/80	−30	−20	Visual field defect worsening, side effects (bradycardia)

Although we found no correlation between the decrease in blood pressure and worsening of the visual field defects, frequent measurement of the blood pressure and testing of the visual field is desirable during this treatment, especially when the blood pressure is lower than expected for the age of the patient and if the decrease in blood pressure caused by propranolol is more than moderate.

In patients with glaucoma, addition of propranolol to conventional antiglaucomatous therapy may help keep the IOP down for periods of up to 3.5 years. Although beta-adrenergic blocking agents have contraindications, propranolol can be considered in the therapy of glaucoma when a satisfactory IOP cannot be achieved by conventional medical therapy.

SUMMARY

In 17 patients with glaucoma and in two with ocular hypertension, all of whom had not responded satisfactorily to any conventional therapy, treatment was extended to include propranolol systemically. In periods up to 3.5 years, this therapy has kept the intraocular pressure at levels below 23 mm Hg in seven patients. Propranolol was withdrawn in five patients whose visual field continually deteriorated. No correlation between worsening of visual field defects and decrease in systemic blood pressure was noted. In the other patients propranolol was withdrawn because of increasing intraocular pressure or side effects.

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LEAKING FILTERING BLEBS

Z. SINNREICH, M.D., R. BARISHAK, M.D., AND R. STEIN, M.D.
Tel-Hashomer, Israel

After successful filtering operations, aqueous humor escapes either by a subconjunctival or a transconjunctival route. The subconjunctival route involves resorption of the aqueous by the conjunctival vessels or by the deep venous plexus of the sclera.[1] The transconjunctival route implies the oozing of aqueous through the bleb[2]; permitting the aqueous to seep to the conjunctival surface and to mix with the tears. Spontaneous filtering blebs that occur after cataract extraction behave the same as filtering blebs.

In some cases in the early postoperative period aqueous leaks temporarily because of incomplete closure of the conjunctival wound or an inadvertently buttonholed conjunctiva. In others the leakage becomes permanent and is accompanied by hypotony and eventually a shallow anterior chamber. Clinically, as may be seen with Seidel's fluorescein test, the aqueous pours, spontaneously or after some pressure on the eyeball, from a definite site in the bleb. In these cases of permanent leakage, we assumed that some kind of a mechanism prevents the closure of the transconjunctival leak.

To study this mechanism, we examined ten excised leaking blebs sent to the Mitrani Foundation Laboratory of Ophthalmic Pathology between 1965 and 1972.

MATERIAL AND METHODS

The examined specimens included seven blebs that had a permanent leakage after filtering operations; one bleb after a filtering operation with intermittent leakage; and two leaking spontaneous blebs after cataract extraction.

The tissues were paraffin-embedded and serial sections were made. The slides were stained with hematoxylin and eosin, PAS, and Masson's trichrome stains.

The histologic findings in the above material were compared with those of two autopsy eyes that had active filtering blebs after Elliot trephining. Four of the ten cases (Table) are presented in detail.

CASE REPORTS

Case 1—A 60-year-old woman had a flap-sclerotomy with a basal iridectomy in her right eye in 1961. Five years later she complained of blurred vision in the operated eye. A hypotony of 8 mm Hg caused by a leak in the filtering bleb was found. The bleb was excised and the defect covered with a free conjunctival graft. A new filtering bleb developed and no further complications occurred during a three-year follow-up.

Histology (Fig. 1) revealed a thinned conjunctival epithelium, subepithelial edema, and a tract lined by multilayered conjunctival epithelium extending down to the inner surface of the specimen.

Case 2—A 65-year-old man underwent a right ocular Elliot trepanation in 1965 for open-angle glaucoma. Two years later a leaking bleb with marked hypotony (6 mm Hg) was diagnosed.

The histologic examination of the excised bleb revealed a moderate subconjunctival inflammation with homogenization of the collagen in some areas. An epithelial tract extended through the whole thickness of the conjunctiva (Fig. 2).

Case 3—A 60-year-old woman underwent an intracapsular cataract extraction in her right eye in March 1970. Two months later she had a spontaneous leaking bleb. The Seidel test was positive and the intraocular pressure was 10 mm Hg. A small dehiscence of the wound at the base of the bleb could be seen. The bleb was excised and the wound resutured. The conjunctival defect was covered by adjacent conjunctiva. No complications were seen during a two-year follow-up.

The histologic examination of the bleb (Fig. 3) showed the presence of an epithelial tract through the whole thickness of the specimen, a thickened epithelium with invaginations, and subepithelial inflammation.

Case 4—A 70-year-old woman had a cataract ex-

From the Mitrani Foundation Eye Pathology Laboratory, Maurice and Gabriela Goldschleger Eye Institute, the Chaim Sheba Medical Center Tel-Hashomer and the Tel-Aviv University Sackler School of Medicine, Israel.

Reprint requests to Z. Sinnreich, M.D., Department of Ophthalmology, Meir Hospital, Kfar-Saba, Israel.

TABLE

SUMMARY OF CLINICAL AND HISTOLOGIC FINDINGS

Case No.	Age (yrs)	Sex	Clinical Findings: Seidel Test	Clinical Findings: IOP (mm Hg)	Histologic Findings*: Epithelial Tract	Histologic Findings*: Thick Conjunctival Epithelium	Histologic Findings*: Inflammation	Remarks
1	74	F	Positive	14	+	+	+	
2	60	F	Positive	8	+	+	+	
3	71	M	Positive	4	−	+	+	
4	65	M	Positive	6	+		+	
5	61	F	Negative	6	+	+	+	
6	29	M	Positive	6	+	+	+	
7	59	M	Positive	12	+	+	+	
8	47	F	Positive	0-2	−	+	+	Invagination cyst
9	60	F	Positive	10	+	+	+	
10	70	F	Negative	6	+	−	+	

*+Indicates present; −, absent.

traction in her left eye in October 1970. A few days later, a spontaneous filtering bleb was observed. Six months later, she was readmitted because of marked hypotony in this eye (4 to 6 mm Hg). The Seidel test was occasionally positive, but always present when pressure was applied to the eyeball. An unsuccessful attempt was made to close the bleb by cryoapplications. Four months later the bleb was excised and the wound resutured. No complications were observed during a two-year follow-up period.

Histologic examination (Fig. 4) showed a surface conjunctival epithelium of variable thickness with moderate subepithelial inflammation and homogenization of the connective tissue. A tortuous epithelial tract could be followed through the thickness of the conjunctiva and subconjunctiva.

The filtering blebs of the two autopsy eyes showed active blebs (Fig. 5): thin conjunctival epithelium covering cystic edematous tissue, and the inner opening of the bleb lined by a Descemet-like substance and by endothelial cells.

DISCUSSION

The normal filtering bleb appears histologically as a cystic area in an edematous subconjunctival tissue and is connected with the anterior chamber.[2,3] The connection between the anterior chamber and the bleb is lined by a Descemet-like substance and endothelial cells, pigmented



Fig. 1 (Sinnreich, Barishak, and Stein). Conjunctival epithelium lines the tract and partly covers the inner face of the bleb (hematoxylin and eosin, × 120).

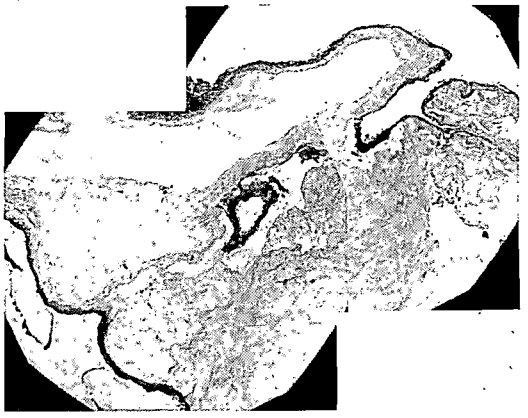


Fig. 2 (Sinnreich, Barishak, and Stein). Tortuous epithelial tract extending through the whole thickness of the bleb (hematoxylin and eosin, ×50).

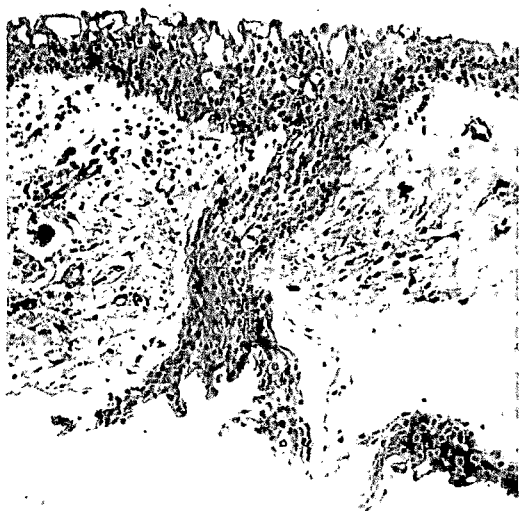


Fig. 3 (Sinnreich, Barishak, and Stein). Epithelial tract extending through the whole thickness of the bleb and lining its inner face (hematoxylin and eosin, ×120).



Fig. 4 (Sinnreich, Barishak, and Stein). Epithelial tract running through the whole thickness of the conjunctiva and covering part of its inner face (hematoxylin and eosin, ×50).



Fig. 5 (Sinnreich, Barishak, and Stein). Functional filtering bleb, following an Elliot trepanation. A Descemet-like substance and endothelial cells line its inner aperture (hematoxylin and eosin, ×120).

cells, or both.[4–7] This arrangement permits the percolation of aqueous humor into the subconjunctival space. The lytic action of the aqueous on the connective tissue causes the appearance of subconjunctival edema and of cystoid spaces with marked thinning of the overlying conjunctival epithelium.

Bleb leakage may be caused by traumatic rupture of the bleb,[8] prolonged use of cortico steroids,[8,9] or extreme thinning of the conjunctiva covering the bleb.[10] Duke-Elder[3] stated that

> the most permanent and efficient factor in keeping a patent channel would appear to be the migration of the pigmentary cells of the iris, which being ectodermal are not engulfed in mesodermal overgrowth.

Epithelial cells of the conjunctiva may play a similar role by lining a leaking tract, thus preventing its closure.[6] The tendency of epithelial cells to cover any continuity defect is well documented.[11,12] Conversely, Theobald[13] stated that "epi-

thelial ingrowth has never been reported as occurring in filtering operations." However, the review of our cases shows that the formation of an epithelial tract in leaking blebs is a histologic reality. In eight of our ten cases, we found an ingrowth of the conjunctival epithelium into the subconjunctival tissue. In one case, an invagination cyst was present, and in the last case we could not identify the site of the leakage.

Theobald[13] states that on histologic examination of 14 cases of epithelization of the anterior chamber, only in five cases was she able to trace the epithelial tract through the wound and that "the condition could have been found in the other cases if it had been possible to serial section the entire eye." This method of serial sections enabled us to discover the epithelial tract in the majority of our cases. The epithelial tract was not detected in two cases, perhaps because it was at the edge of the specimen and therefore lost during the first sections of the paraffin block.

The material examined by us consisted only of conjunctiva and subconjunctival tissue as it was sliced off by the surgeon. We were, therefore, unable to determine whether the epithelial ingrowth also involved the corneoscleral limbal opening. Chandler[14] described two aphakic eyes with ruptured filtering blebs that were lost because of epithelization of the anterior chamber. Clinical follow-up did not reveal such an invasion in any of our cases.

In some of our cases of leaking blebs, the Seidel test was negative at the time of testing, but with pressure on the globe, the test became positive. A possible explanation of this finding may be that spontaneous leaking through the wall of the bleb depends on the pressure gradient between the anterior chamber and the conjunctival surface[1,6,15] and also on the amount of fluid present in the anterior chamber. For this reason leaking blebs may not leak if there is a shallow anterior chamber.[16]

Because an epithelial tract running from the conjunctival surface down to the sclera was found in eight of the ten cases, we surmise that this formation is responsible for the persistent leakage of filtering blebs. Because this epithelial tract is an established anatomic structure, conservative treatment can be of no avail. We believe that the only reasonable treatment in these cases is the surgical removal of the bleb[17] and covering of the defect by healthy conjunctiva, thus preventing epithelial downgrowth into the anterior chamber, diminishing the danger of late infection,[18,19] and eliminating the harmful effects of hypotony.

SUMMARY

Histologic examination of ten leaking filtering blebs revealed an epithelial tract running from the surface of the bleb down to the episclera in eight cases. These epithelial tracts were considered the real cause of the persistent leakage.

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OPHTHALMIC MINIATURE

The doctor had moved to the nearest crate and, with stolid competence, was prying off the lid.

"The first thing we do is fit you out competently. Oh! I know you two believe in God. And the Lieutenant in Confucius." He bent and produced rubber boots from the case. "But I believe in prophylaxis."

He completed the unpacking of his supplies, fitting white overalls and goggles upon them, berating their negligence of their own safety. His remarks ran on, matter-of-fact, composed. "Don't you realize, you confounded innocents. . . one cough in your eye and you're done for. . . penetration of the cornea. They knew that even in the fourteenth century. . . they wore vizors of isinglass against this pneumonic plague. . . it was brought down from Siberia by a band of marmoset hunters."

A. J. Cronin, *The Keys of the Kingdom*
Victor Gollancz, 1942

VITREOUS FINDINGS IN FELLOW EYES OF APHAKIC RETINAL DETACHMENT

KENNETH R. HOVLAND, M.D.
Denver, Colorado

Whether the occurrence of posterior vitreous separation is spontaneous or follows trauma or inflammation, it may represent the most critical event relating to retinal detachment.

I believe that if posterior vitreous separation occurs without forming a tear, the risk of retinal detachment decreases significantly. To evaluate this point, I studied the fellow eyes of patients with aphakic retinal detachment. The well documented risk of retinal detachment is 20 to 30% in such fellow eyes.[1-3] Few of the studies, however, have attempted to relate vitreous separation to retinal detachment. I examined 100 patients with aphakic retinal detachment to see if the presence of posterior vitreous separation in the fellow eye was prognostically significant.

SUBJECTS AND METHODS

My study included 100 patients with (1) bilateral aphakia; (2) primary rhegmatogenous retinal detachment in one or both eyes; (3) adequate visualization of the retina and vitreous in the fellow eye; and (4) six-month follow-up starting at the time of initial referral and examination for the retinal detachment. Patients with congenital cataract, intraocular lens, intraocular foreign body, and trauma were excluded.

Retinal examination with indirect ophthalmoscopy and scleral depression was performed in each eye, as well as vitreous examination with Goldmann three-mirror lens and Haag-Streit slit lamp. The Hruby lens did not give adequate vitreous detail.

From the Division of Ophthalmology, University of Colorado Medical Center, Denver, Colorado.
Reprint requests to Kenneth R. Hovland, M.D., 508 Republic Building, Denver, CO 80202.

RESULTS

The patients ranged in age from 43 to 86 years, with an average age of 65 years. There were 57 men and 43 women. Follow-up time ranged from six months to nine years, with an average time of four years. The total time lapse since cataract surgery in the fellow eye ranged from one to 23 years, with an average of 7.5 years. Because approximately one half of the retinal detachments occur in the first year after cataract surgery,[1] this follow-up period appeared to be adequate.

In the fellow eyes, posterior vitreous separation without retinal tear was present in 43 patients. Posterior vitreous separation with a retinal tear or detachment was present in 17 patients. Posterior vitreous separation was not evident in 40 of the patients (Table 1).

Of the 43 patients who had posterior vitreous separation without a tear, only a 65-year-old man, who was initially examined for rhegmatogenous retinal detach-

TABLE 1

FELLOW EYES IN PATIENTS WITH APHAKIC RETINAL DETACHMENT

Vitreous Findings	No. of Eyes
PVS*, without retinal tear	43
PVS*, with retinal tear and detachment	17
No evident PVS*	40
Total	100

*PVS designates posterior vitreous separation.

ment in the left eye, later developed retinal detachment. The right eye was found to have posterior vitreous separation without retinal break. However, 11 months later, the patient noted a shadow and was found to have a superotemporal retinal detachment with several peripheral horseshoe tears. The detachment did not reach the macula and visual acuity of 6/7 (20/23.3) was regained following the scleral buckling procedure.

Of the 17 patients who had posterior vitreous separation and retinal tear or detachment, five had definite retinal detachment and 12 had retinal tears. All were successfully treated. None of these patients later developed new retinal breaks. At least seven of the 17 patients had tears that were best seen with scleral depression and indirect ophthalmoscopy, but poorly or not at all with the three-mirror lens.

Of the 40 patients who did not show evidence of posterior vitreous separation initially, 11 later developed symptomatic posterior vitreous separation, eight of whom developed retinal detachment. Detachment in these patients occurred at various times, ranging from four months to six years after initial examination (but in a few days after the manifestation of the symptoms of posterior vitreous separation in each instance). The other three patients developed posterior vitreous separation without tear or detachment. None of the 11 had only retinal tear. Two of the patients had undergone prophylactic laser coagulation to areas of lattice degeneration with holes, but this failed to prevent retinal detachment when posterior vitreous separation occurred and breaks formed in areas of minimally abnormal retina. One patient developed a giant retinal tear in the fellow eye, which was not successfully reattached. Of the remaining seven retinal detachments, only one had reached the macula. These were successfully repaired, with preservation of good vision.

Each group had similar age range and elapsed time after cataract surgery. Although vitreous loss increases the risk of retinal detachment, there were too few cases of such an event in this series to relate retinal detachment to either direct vitreous loss or late rupture of the anterior vitreous face. Similarly, there were too few cases of extracapsular procedures to be significant. Each group had similar refractive range.

Of the 100 original retinal detachment eyes, 95 were successfully attached. Of the five failures, four had total retinal detachment, horseshoe tears with rolled edges, and questionable posterior vitreous separation.

Discussion

Of the original 43 fellow eyes that had posterior vitreous separation and no retinal break, only one subsequently developed retinal detachment. However, of the 40 fellow eyes without posterior vitreous separation, eight subsequently developed retinal detachment (Table 2). The P value of this relationship, using Fisher's exact test, is .01.

Thus, if the vitreous and retina in the fellow eye of a patient with aphakic retinal detachment can be seen well and posterior vitreous separation is present

TABLE 2

LATER OCCURRENCE OF APHAKIC RETINAL DETACHMENT IN FELLOW EYES*

Initial Vitreous Findings	No ARD	Later ARD
PVS, without retinal tear	42	1
No evident PVS	32	8
		P = .01

*ARD designates aphakic retinal detachment; PVS, posterior vitreous separation.

without retinal tear, much greater assurance can be given to the patient that subsequent retinal detachment will not develop. This knowledge not only may benefit the patient psychologically, but also may help in decisions regarding whether or not to proceed with retinal or vitreous surgery in the first eye if there is only minimal hope of reattachment.

Often the breaks in aphakic retinal detachment are small tears at the posterior margin of the vitreous base and act pathophysiologically as horseshoe tears. These can be detected by using indirect ophthalmoscopy with scleral depression or by following the posterior vitreous face to its junction with the retina at the vitreous base.[4] In the 17 patients who revealed tear or detachment in the fellow eye on initial examination, many of the breaks were only visible with scleral depression. Thus, one cannot completely rely on a three-mirror lens examination to rule out the presence of retinal breaks. The classification of a patient in the low-risk group following posterior vitreous separation largely depends on a thorough examination with indirect ophthalmoscopy and scleral depression that gives negative results.

A possible explanation for the one patient who later developed aphakic retinal detachment in the posterior vitreous separation group would be an initial lack of peripheral separation of the vitreous gel all the way to the ora serrata. Even with detailed vitreous examination, one cannot be certain that the vitreous gel has completely separated from the retina for 360 degrees, especially in the lower quadrants. Nevertheless as evidenced in the cases in this study, most aphakic retinal tears occur at the time of posterior vitreous separation or shortly thereafter (namely, days).

The vitreoretinal adhesion in areas of lattice degeneration is so strong that posterior vitreous separation peripheral to such areas rarely occurs. Retinal detachment most often occurs from tears at the posterior margin or sides of such patches,[5] rather than from the round holes within the patch, except in young myopic individuals with multiple atrophic retinal holes.[6] Consequently, the risk of retinal detachment in eyes with visible lattice and posterior vitreous separation may remain high, although this is not shown in the present study. The instructions to the patient are obviously the same in all groups, namely, to report sudden flashes, floaters, or shadows.

There are apparently two major subgroups in the fellow eyes of patients with aphakic retinal detachment. (1) Posterior vitreous separation has occurred without retinal tear, and the risk of developing retinal detachment is low (2%). (2) Posterior vitreous separation has not yet occurred and the risk of subsequent retinal detachment is high (at least 20%).

This decreased risk following posterior vitreous separation may also apply to phakic eyes, but there are many more variables, such as myopia, trauma, and inflammation.

SUMMARY

One hundred patients had bilateral aphakia, primary rhegmatogenous retinal detachment, and adequate visualization of the retina and vitreous in the fellow eye. Of 43 patients with posterior vitreous separation and no retinal tear in the fellow eye, only one (2%) subsequently developed retinal detachment. Of 40 patients without posterior vitreous separation in the fellow eye, eight (20%) later developed retinal detachment following posterior vitreous separation. The remaining 17 patients had posterior vitreous separation and retinal tear or detachment at the time of initial examination. Thus, if posterior vitreous separation oc-

curs without forming retinal tear, the risk of developing retinal detachment is significantly lowered.

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OPHTHALMIC MINIATURE

It is unfortunate that the hammer has become such a symbol of geology; a hand lens would be at least as appropriate. A total ban on the use of hammers on some sites is clearly neither necessary nor desirable at some sites, but a severe restriction of the numbers of hammers used by large parties would save the exposures themselves, protect access to them, would save some ghastly injuries, especially to eyes, and could be a considerable advance in the training of geologists.

Brian Lovell, *New Scientist*
Grant Institute of Geology
University of Edinburgh, December 1977, p. 817

RETINAL HOLES

ROBERT Y. FOOS, M.D.
Los Angeles, California

Holes of the peripheral retina are full-thickness breaks, trophic in origin, that have no associated flap or free operculum.[1-6] In recent years increasing experience with diseases of the peripheral retina in our laboratory has revealed that primary retinal holes (those with no indication of a proximal cause and no lattice degeneration in either eye) are remarkably rare and that most holes occur as complications of other lesions. Eyes taken at autopsy provided the material for a detailed analysis of primary retinal holes and a tabulation of the lesions that secondarily develop retinal holes.

MATERIAL AND METHODS

Both eyes from 2,800 subjects autopsied at the UCLA Center for the Health Sciences and the Los Angeles County Harbor General Hospital were used in this study; 2,242 (78%) subjects were 20 years of age or older at death; 1,290 (46.1%) were female. Cases were excluded when thorough examination was prevented by the following: retinal detachment of obscure cause (six cases), opaque media (three cases), and severe autolysis (two cases). Racial information was available in 2,741 cases: white (81%), black (18%), and Oriental (1%).

Sixty-eight subjects (97 eyes) in this series had been operated on for cataracts. However, seven of these cases (eight eyes) were excluded from the study because of retinal detachment (the cause of which was unknown in five eyes) related to traction from vitreous incarceration in a corneal wound in one eye, caused by traction from proliferative diabetic retinopathy in one eye, and related to lattice degeneration in one eye. Thus, there remained a total of 89 eyes available for a separate analysis of retinal holes in surgically aphakic specimens.

Preparation, gross-sectioning, macroexamination, recording of findings, and histopathologic examinations were performed according to our routine methods.[7]

RESULTS

In our laboratory retinal holes are considered primary only when there is no other identifiable lesion near the hole, and when lattice degeneration is absent in the involved eye and in the fellow eye.[8,9] All other holes are considered secondary and are classified according to the features of the proximally related lesion or to the associated process in the same or in the fellow eye.

Macroscopic features—Primary retinal holes were found in the basal zone of the peripheral retina,[10] and appeared as round to ovoid full-thickness breaks whose margins were uniformly smooth and lacking in vitreous condensations (Figs. 1 and 2). The margins, however, occasionally developed slight microcystic change, but the retina immediately surrounding the hole was always free of peripheral cystoid degeneration. Although retinal detachment was relatively common, it was invariably localized to a region less than 0.5 disk diameter in greatest dimension. The underlying pigment epithelium was usually granular, stippled, or, rarely, blotchy.

Secondary holes were also round to ovoid, but their margins were slightly

From the Department of Pathology and the Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles, California. This study was supported in part by United States Public Health Service research grants EY 00331, EY 01090, and EY 00725 from the National Eye Institute, National Institutes of Health.

Reprint requests to Robert Y. Foos, M.D., Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles, CA 90024.

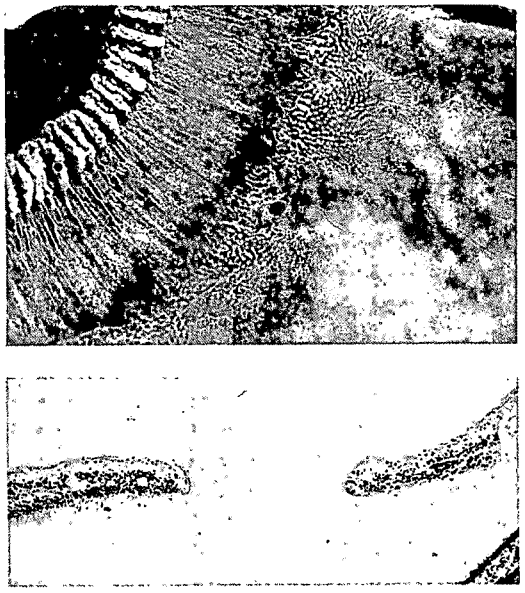


Fig. 1 (Foos). Primary retinal hole (Case 3, Table 2). Top, Round, full-thickness retinal break immediately behind ora serrata is located within vitreous base in otherwise unremarkable retina between two regions with typical cystoid degeneration (×9). Bottom, Microsection through hole shows complete loss of retinal tissue and slight disorganization of adjacent retina (especially notable anteriorly, on right). Loss of photoreceptor cell outer segments of immediately adjacent retina is an indication of slight retinal detachment.



Fig. 2 (Foos). Primary retinal hole (Case 8, Table 2). Top, slightly ovoid full-thickness break is located in basal zone of peripheral retina. Immediately surrounding hole, the retina is slightly elevated and degenerated (×17). Bottom, Microsection through hole shows loss of neuronal elements and nonspecific degeneration of retina adjacent to the break. Retina at posterior margin of break (arrow) was adherent to pigment epithelium, but was artifactually detached in processing. Longstanding localized retinal detachment is indicated by loss of both outer and inner segments of retina anterior to break and by degenerative changes of underlying pigment epithelium. Pigmented cellular debris in overlying vitreous is an indication of recent degenerative changes in region (hematoxylin and eosin, ×80).

irregular in certain categories of parent lesions, most notably in holes related to chorioretinitis, zonular traction tufts,[11] or meridional folds[1,12] (Figs. 3-5). Also, such features as vitreous changes, degenerative changes of the surrounding neurosensory retina, and marked degeneration of the associated pigment epithelium were common, again depending on the cause and the character of the primary lesion.

Microscopic features—Primary retinal holes show few characteristic microscopic features. The margins were usually smooth, but there were no consistent changes in the proximal retina (Figs. 1 and 2). Virtually all showed some changes related to localized retinal detachment, with loss of photoreceptor cell outer segments and nonspecific degenerative changes of the underlying pigment epithelium. The underlying choroid, however, contained no consistent or specific alteration.

Secondary retinal holes showed degenerative or inflammatory features according to the nature of the causative lesion (Fig. 5).

Statistical data—Retinal holes were found in 111 (4%) of the 2,800 subjects (129 adult subjects, 5%); they were bilat-

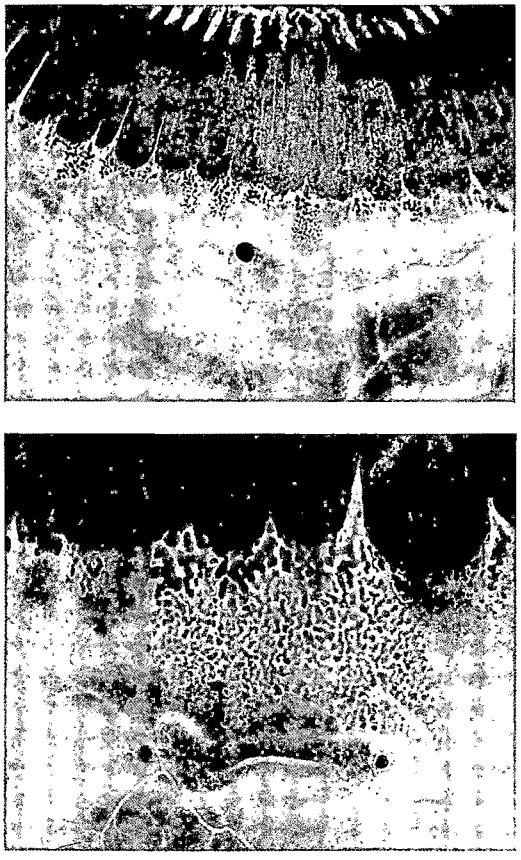


Fig. 3 (Foos). Hole in anteriorly located lattice degeneration (vitreous base excavation) simulating primary retinal hole. Top, Round hole in retina has almost obliterated the parent lattice lesion (ovoid excavation with long axis parallel to ora serrata and with slightly elevated margins) (×7.3). Bottom, Lattice degeneration (with a hole in each end) in retina adjacent to excavation shown in Figure 3, top, is one of seven typical lattice lesions in this and the fellow eye (×12).

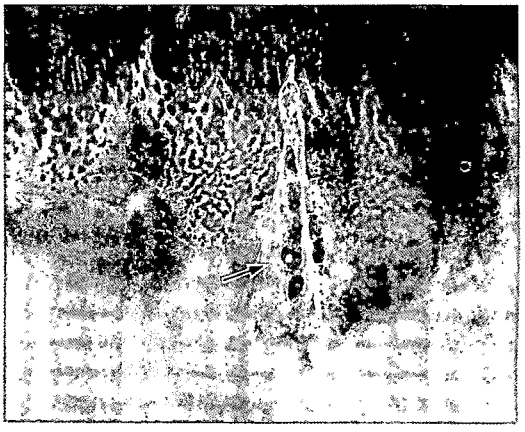


Fig. 4 (Foos). Holes in base of zonular traction tuft. A characteristic large tuft within vitreous base extends over the ora serrata toward ciliary body. Tuft has typical "goose foot" posterior base, in which there are four holes; two of these have become confluent (arrow) (×16).



Fig. 5 (Foos). Chorioretinitis with retinal holes. Top, Large equatorial lesion shows irregular retinal thinning, conspicuous dendritic pigmentation of retina and retinal holes (arrows). Bottom, Microsection through larger hole shows gliosis and adherence of both margins to underlying intact Bruch's membrane. The underlying choroid in this healed lesion has partial obliteration of choriocapillaries and fibrosis (hematoxylin and eosin, ×125).

eral in 25 (23%); thus, holes were present in 136 (2.4%) of the 5,600 eyes.

Primary retinal holes were found in only eight of the 136 eyes with retinal holes (Table 1). All occurred in eyes from subjects who were late-middle-aged or elderly, but who had no characteristic systemic disease. All holes were unilateral, single, and within the basal zone of the peripheral retina (Table 2). There was neither consistent quadrant predilection

TABLE 1

RETINAL HOLES

	No. of Eyes	%
Primary	8	6
Secondary		
Causes		
Lattice degeneration	103	76
Postinflammatory	9	7
Zonular traction tufts	10	7
Meridional folds	3	2
Pavingstone degeneration	2	1
Miscellaneous	1	<1
Total	136	

nor association with posterior vitreous detachment. The holes ranged in dimension from 0.1 to 0.4 mm. All lesions showed evidence of slight and localized retinal detachment.

Secondary retinal holes were present in 128 eyes (2.3%) and were caused by lattice degeneration in 103 eyes; zonular traction tufts in ten; chorioretinitis in nine; meridional folds in two; pavingstone degeneration in two; and an unclassified disorder in one. In lattice degeneration the holes were sometimes multiple. All the zonular traction tufts with holes of the retina at their base were single and unilateral; only two lesions had multiple holes, both having a single large tuft with two separate holes in the bases. All other eyes with secondary holes had only one lesion and a single hole in each.

TABLE 2

PRIMARY RETINAL HOLES*

Case No.	Age,Sex (yrs)	Quadrant†	PVD‡	Size (mm)
1	74,M	LT	N	0.2
2	74,M	LN	P	0.1
3	60,M	UT	N	0.4
4	69,F	UT	N	0.3
5	57,F	UT	N	0.3
6	71,M	UN	C	0.3
7	53,F	LN	N	0.3
8	58,M	LT	N	0.3

*All primary holes occurred singly in the eight subjects and in eyes; all were found in the basal zone.

†L designates lower; U, upper; T, temporal; N, nasal.

‡PVD designates posterior vitreous detachment; N, no posterior vitreous detachment; P, partial posterior vitreous detachment; and C, complete posterior vitreous detachment.

The 89 surgically aphakic eyes showed no primary holes. Secondary holes (all single) were noted in four eyes and were caused by lattice degeneration in three eyes and pavingstone degeneration in one eye. This rate of occurrence did not differ significantly from that in the phakic patients.

DISCUSSION

Primary retinal holes are rare in the peripheral retina, which relates directly to the terms used to define a primary retinal hole. However, the necessity of excluding lattice degeneration in the definition cannot be overemphasized. Lattice degeneration is extremely polymorphous and the most experienced observer can misinterpret some lattice lesions, especially when consideration is not given to findings in other parts of the peripheral fundus or in the fellow eye (Fig. 3).

As a cause of retinal detachment, primary retinal holes must be discounted as a significant lesion, not only because of their statistical rarity, but also because they almost always occur within the vitreous base,[10] where full-thickness breaks rarely cause significant retinal detachment.

On the other hand, retinal detachment often occurs in eyes with lattice degeneration,[8,9,13,14] the most common cause of secondary retinal holes in this study. In this regard, the recent report by Byer,[13] who had excellent follow-up information, discounted holes in lattice lesions as a significant cause of retinal detachment in phakic patients who have not had detachment in their fellow eyes. One therefore

must conclude that the retinal tear, the other full-thickness break of the peripheral fundus, is the major cause of retinal detachment in patients with lattice degeneration. However, for those who would risk prophylactic treatment of lattice lesions, it should be emphasized that retinal tears in eyes with lattice degeneration usually do not involve the lesion itself, but occur as juxtabasal tears[15] at unpredictable sites distant from recognized lattice lesions.[13,15]

Regarding the other causes of secondary retinal holes, two lesions, zonular traction tufts and meridional folds, occur predominantly within the vitreous base and are therefore less significant. Two other causes, postinflammatory lesions and pavingstone degeneration, virtually always culminate in strong retinochoroidal adhesions and thus, their holes are unlikely to lead to retinal detachment. Peripheral cystoid degeneration is never a cause of full-thickness retinal breaks.

SUMMARY

Holes of the peripheral retina, defined as full-thickness breaks of trophic origin with no associated flap or free operculum, were found in 136 (2.4%) eyes from 2,800 autopsied subjects. Primary retinal holes (those with no indication of a proximal causative lesion and with no lattice degeneration in either eye) occurred in only eight of the 5,600 eyes studied; all were unilateral, single, less than 0.25 disk diameter in size, within the basal zone, and in eyes from elderly subjects. Secondary holes were found in 128 (2.3%) of eyes and of these, lattice degeneration was the most common cause (103). Other lesions complicated by hole formation included zonular traction tufts (10), chorioretinitis (9), meridional folds (3), and pavingstone degeneration (2). Retinal holes in surgically aphakic eyes did not differ qualitatively or quantitatively from those in age-matched phakic eyes.

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IN VITRO ANTIBIOTIC SYNERGISM AGAINST OCULAR FUNGAL ISOLATES

GEORGE A. STERN, M.D.
San Francisco, California

The development of the polyene antifungal agents amphotericin B and natamycin improved the prognosis of ocular fungal infections. Nonetheless, approximately 18% of the cases of fungal keratitis still require therapeutic surgical intervention.[1,2] Fungal endophthalmitis is an even more serious problem. Experimental studies[3,4] have shown that the polyene antibiotics penetrate the eye poorly, if at all, and they have thus failed to improve materially the poor prognosis of intraocular fungal infections. The imidizole derivatives (clotrimazole, miconazole, and econazole) may ultimately greatly improve antifungal therapy,[5] but in this country they are investigational agents. Advances in the antimicrobial therapy of ocular fungal infections require the development of new, more effective drugs or more effective ways of using the drugs we have. The use of synergistic combinations of antibiotics is one promising possibility.

We have learned recently that low levels of amphotericin B potentiate the action of certain antibiotics against some species of fungi. In vitro experiments have shown, for example, that amphotericin B potentiates the action of mycophenolic acid glucuronide, tetracycline, and actinomycin D against *Saccharomyces cerevisiae*,[6] and potentiates the action of rifampin against *Candida albicans*,[7] other *Candida* species,[8] *Histoplasma capsulatum*,[9,10] *Aspergillus*,[11] and *Coccidioides immitis*.[12] Synergism has also been demonstrated between amphotericin B and 5-flucytosine when combined against several yeasts[13] and some strains of *Aspergillus*,[11] and between amphotericin B and tetracycline[14] against *C. albicans*. In vivo studies have shown that combined amphotericin B-tetracycline therapy is more effective against murine coccidioidomycosis[15] than amphotericin B alone, and that combined amphotericin B-rifampin therapy is more effective against murine histoplasmosis and blastomycosis than amphotericin B alone.[16] In one recently reported[17] human case, *Candida* endophthalmitis was cured with combined amphotericin B-rifampin therapy.

To date there are no published reports of synergism between antibiotics when combined to treat oculopathogenic fungi. We variously combined and tested in vitro two polyene antifungal agents (amphotericin B and natamycin) and four antibiotics (rifampin, tetracycline, gentamicin, and clindamycin) for their synergistic effect on 28 ocular fungal isolates.

MATERIAL AND METHODS

Organisms—The organisms used in the study were divided into the following three groups: Group 1: *Candida* species and other yeasts; Group 2: *Fusarium solani*; and Group 3: other filamentous fungi (Table 1). The ocular or periocular sites from which the organisms were isolated are listed (Table 2). The identified organisms were transferred only as often as necessary to preserve their viability. Fungi recovered from patients after the study was begun were tested as soon as they could be isolated in pure culture.

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Reprint requests to George A. Stern, M.D., Department of Ophthalmology, George Washington University School of Medicine, 2150 Pennsylvania Ave., N.W., Washington, DC 20037.

TABLE 1
IDENTIFICATION AND NUMBER OF ORGANISMS TESTED

Genus and Species of Fungi	No. of Isolates
Group 1—*Candida* and other yeasts	
C. albicans	5
C. parapsilosis	3
C. krusei	1
Rhodotorula species	1
Group 2—*Fusarium*	
F. solani	10
Group 3—Other filamentous fungi	
A. niger	2
A. fumigatus	1
Penicillium species	1
Rhizopus species	2
P. lilacinus	1
S. brevicaulis	1

The others had been lyophilized and were reconstituted when needed, except the *Fusarium* isolates, which were maintained on Sabouraud-dextrose agar under a layer of mineral oil.

Preparation of organisms—The organisms in Groups 1 and 3 were grown at room temperature on slants of Sabouraud-dextrose agar. Strains of *F. solani* (Group 2) were grown at room temperature on potato agar slants to encourage sporulation. The slants were incubated long enough to allow adequate numbers of yeast cells or conidia to form (usually 48 hours for strains in Group 1, three to four days for strains in Group 3, and five to seven days for strains in Group 2). The slants were then washed with sterile normal saline solution to which 1% polysorbate 80 was added to prevent clumping of conidia. To determine the concentration of conidia or yeast cells in the washings, we counted them in a hemocytometer and adjusted them to a concentration of 4,000,000/ml. The rare hyphal fragments seen in the washings, which represented potential colony-forming units, were included in the count, and in the case of *Fusarium*, both microconidia and macroconidia were counted.

TABLE 2
OCULAR OR PERIOCULAR SOURCE OF FUNGAL ISOLATES

Source of Organism	No. of Isolates
Group 1—*Candida* and other yeasts	
Conjunctiva or eyelid	7
Corneal ulcer	2
Endophthalmitis	1
Group 2—*Fusarium*	
Corneal ulcer	10
Group 3—Other filamentous fungi	
Corneal ulcer	4
Endopthalmitis	1
Conjunctiva	1
Lacrimal apparatus	1
Infected scleral buckle	1

Preparation of antibiotic-impregnated disks—The two polyene agents amphotericin B and natamycin were dissolved in methanol. Two antibiotics, rifampin and tetracycline, were also dissolved in methanol, and the two others, gentamicin sulfate and clindamycin HCl, were dissolved in water. The solutions were adjusted to appropriate concentrations, and 20 μl of each solution was applied to 6.35-mm blank filter paper disks. The solvents were allowed to evaporate and the disks were stored at 4° C. Preliminary studies indicated that the fungal sensitivities were the same whether the antibiotic was added in the form of drug-impregnated disks or directly to the solution. Periodic checks by an agar diffusion method against susceptible test strains of *C. albicans* or *S. epidermidis* indicated that there was no loss of activity from the disks over the period of the experiment.

Fungal sensitivities and definition of drug interactions—The minimal inhibitory concentrations and minimal fungicidal concentrations of amphotericin B and natamycin were determined by a modifi-

cation of the microtiter method for the determination of fungal sensitivities described by Polansky, Robinson, and Jones.[18] Similar determinations were then made after the addition of 25 μg/ml of each of the four antibiotics: rifampin, gentamicin, clindamycin, and tetracycline. No organisms tested were found to be inhibited by 250 μg/ml of any one of the antibiotics. The concentration of the antibiotics used was therefore less than one tenth of the minimal inhibitory concentration and was assumed to have no effect.

All tests were performed in duplicate. The results rarely differed by more than one dilution, and when such a difference occurred, the results were averaged. A fourfold reduction in the minimal inhibitory concentration, minimal fungicidal concentration, or both, of an antifungal agent in the presence of an antibiotic was considered synergism; a fourfold increase in the minimal inhibitory concentration, minimal fungicidal concentration, or both, was considered antagonism; and less than a fourfold change in the minimal inhibitory concentration and minimal fungicidal concentration was considered indifference.

Determination of sensitivities—In all of the studies, yeast nitrogen base broth with L-asparagine and 1% dextrose was the fungal culture medium. One milliliter of broth and a 50-μl inoculum containing 200,000 yeast cells or conidia was placed into each well of culture medium in clear plastic multiwell plates. Antibiotics were then added in the form of antibiotic-impregnated filter paper disks containing serial twofold dilutions of amphotericin B ranging from 50 μg to 0.1 μg (or 0.05 μg for strains of *C. albicans*) and of natamycin ranging from 25 μg to 0.2 μg. The organisms were also screened for their sensitivity to the four antibiotics at a level of 250 μg/ml by the addition of disks containing 250 μg of each antibiotic. A control well to which no antibiotic or antifungal agent was added was included in each study.

As soon as there was sufficient growth in a control well to be interpretable (usually after 36 hours), the results in the test wells were read. The minimal inhibitory concentration was defined as the lowest concentration of an antifungal agent at which there was no visible growth or turbidity. The minimal fungicidal concentration, which was determined by subculturing the clear wells on Sabouraud-dextrose agar, was defined as the concentration at and above which there was no growth on subculture. Drug interaction studies were performed in the same way except that an additional disk containing 25 μg of antibiotic was placed in each well.

Killing-curve studies—To compare the described method with a standard method, we attempted to correlate it quantitatively with the results of killing-curve studies performed with a strain of *C. albicans* and a strain of *C. parapsilosis*. Synergism between amphotericin B and rifampin had been demonstrated against both these strains when tested by our method. To 10 ml of yeast nitrogen base broth with L-asparagine and 1% dextrose, 2×10^6 organisms were added. Against the strain of *C. albicans*, several concentrations of amphotericin B (1.6 μg/ml, 0.4 μg/ml, and 0.1 μg/ml) were used both with and without 25 μg/ml of rifampin. Control tubes consisted of one tube of yeast nitrogen base broth alone, and one containing 25 μg/ml of rifampin without amphotericin B. The concentrations of amphotericin B used against the strain of *C. parapsilosis* were 50 μg/ml, 3.12 μg/ml, and 0.4 μg/ml, both with and without 25 μg/ml of rifampin. Tubes were incubated at room temperature on a rotary platform, and the organisms were count-

ed at 0, four, eight, and 24 hours by culturing serial 10^{-2} dilutions on trypticase soy agar. The entire study was performed in duplicate. Because the organism counts from each tube were also performed in duplicate, the final organism count was an average of four determinations.

RESULTS

Fungal sensitivities—The sensitivities of the organisms to amphotericin B and natamycin are shown (Table 3). With the methods used in this study, these results were reproducible and consistent with the results of previous studies in which other methods were used.[5,19,20] On a weight basis, amphotericin B was more effective than natamycin against most organisms in Group 1, and natamycin was considerably more effective than amphotericin B against isolates of *F. solani*. In Group 3, natamycin was more effective against the strain of *Penicillium*, one of the two strains of *A. niger*, one of the two strains of *Rhizopus*, and the strain of *Scopulariopsis brevicaulis*. Amphotericin B was more effective against one of the strains of *A. niger* and one of the strains of *Rhizopus*. The strain of *A. fumigatus* was equally sensitive to amphotericin B and natamycin.

Drug interaction studies—GROUP 1: According to the criteria used in the study, there was synergism between amphotericin B and rifampin against 90% of the organisms in Group 1, between amphotericin B and gentamicin against 20%, and between amphotericin B and clindamycin against 10% (Table 4). There was no synergism between amphotericin B and tetracycline, and against 30% of the strains this combination was antagonistic. With one exception, all of the combinations of natamycin and the antibiotics reacted indifferently against Group 1 organisms; the exception was one strain of *C. albicans* against which the combination of natamycin and rifampin was synergistic. Against the organisms in Group 1, the amphotericin B-rifampin combination was clearly the most effective

TABLE 3

MINIMAL INHIBITORY CONCENTRATIONS OF AMPHOTERICIN B AND NATAMYCIN WHEN TESTED IN VITRO AGAINST 28 FUNGAL ISOLATES*

Organism	Amphotericin B		Natamycin	
	Mean MIC (μg/ml)	Range (μg/ml)	Mean MIC (μg/ml)	Range (μg/ml)
Group 1 (10 isolates)				
C. albicans	0.36	0.2-0.6	3.27	1.56-4.68
C. parapsilosis	2.35	0.8-3.12	5.20	4.68-6.25
C. krusei	1.56	1.56	1.56	1.56
Rhodotorula species	6.25	6.25	2.34	2.34
Group 2 (10 isolates)				
F. solani	20.2	3.12-50	4.21	3.12-6.25
Group 3 (8 isolates)				
A. fumigatus	3.12	3.12	3.12	3.12
A. niger	4.30	2.34-6.25	2.34	1.56-3.12
Penicillium species	4.68	4.68	2.34	2.34
P. lilacinus	4.68	4.68	9.37	9.37
Rhizopus species	Undetermined	2.34->50	9.37	6.25-12.5
S. brevicaulis	>50.0	>50.0	3.12	3.12

*MIC designates minimal inhibitory concentration.

TABLE 4

DRUG INTERACTIONS AGAINST TEN ISOLATES OF *Candida* AND OTHER YEASTS*

Drug Combination†	Synergism MIC Only	Synergism MFC Only	Synergism Both MIC and MFC	Total Synergism (%)	Antagonism (%)
AB + R	5/10	2/10	2/10	90	0
AB + G	2/10	0	0	20	0
AB + C	1/10	0	0	10	0
AB + T	0	0	0	0	30
NAT + R	0	1/10	0	10	0
NAT + G	0	0	0	0	0
NAT + C	0	0	0	0	0
NAT + T	0	0	0	0	0

*MIC designates minimal inhibitory concentration; MFC, minimal fungicidal concentration.
†AB designates amphotericin B; NAT, natamycin; R, rifampin; G, gentamicin; C, clindamycin; T, tetracycline.

($P<.01$), and it was more effective than either antifungal drug used alone ($P<.01$).

GROUP 2: When amphotericin B and rifampin were combined, they acted synergistically against eight (80%) of the ten isolates of *F. solani* (Table 5). Because the minimal inhibitory concentration of amphotericin B was reduced in each instance and the minimal fungicidal concentration in only one, fungal growth was predominantly inhibited, but fungal killing was not enhanced. When amphotericin B was combined with other antibiotics, the results were indifferent except for synergism between amphotericin B and gentamicin against one strain, and antagonism between amphotericin B and tetracycline against another. Again, rifampin and amphotericin B was the most effective combination tested ($P<.01$).

When combined, natamycin and rifampin acted synergistically against 70% of the organisms, natamycin and gentamicin against 40%, and natamycin and tetracycline against 20%. The natamycin-clindamycin combination resulted in indifference only. As was the case with the amphotericin B-antibiotic combinations, rifampin was the most effective antibiotic when combined with natamycin. Synergism between natamycin and rifampin was significantly more frequent than it

TABLE 5

DRUG INTERACTIONS AGAINST TEN ISOLATES OF *Fusarium solani**

Drug Combination†	Synergism MIC Only	Synergism MFC Only	Synergism Both MIC and MFC	Total Synergism (%)	Antagonism (%)
AB + R	7/10	0	1/10	80	0
AB + G	1/10	0	0	10	0
AB + C	0	0	0	0	0
AB + T	0	0	0	0	10
NAT + R	1/10	6/10	0	70	0
NAT + G	0	4/10	0	40	0
NAT + C	0	0	0	0	0
NAT + T	0	2/10	0	20	0

*MIC designates minimal inhibitory concentration; MFC, minimal fungicidal concentration.
†AB designates amphotericin B; NAT, natamycin; R, rifampin; G, gentamicin; C, clindamycin; T, tetracycline.

was between natamycin and either clindamycin ($P<.01$) or tetracycline ($P<.03$), but there was no significant difference in this respect between rifampin and gentamicin. In contrast to the interaction between amphotericin B and rifampin, synergistic combinations of natamycin and antibiotics effected enhancement of fungal killing rather than inhibition of fungal growth.

The minimal inhibitory concentration of combined amphotericin B and 25 μg/ml of rifampin was less than or equal to the minimal inhibitory concentration of natamycin alone when tested against 80% of the *Fusarium* strains ($P<.05$), and less than or equal to the minimal inhibitory concentration of combined natamycin and rifampin when tested against 60% of the strains (not statistically significant). In only one case, however, was the minimal fungicidal concentration of the amphotericin B-rifampin combination lower than the minimal fungicidal concentration of natamycin alone, and in no case was it lower than the minimal fungicidal concentration of the natamycin-rifampin combination. On a weight basis, the amphotericin B-rifampin combination was thus more effective in inhibiting fungal growth, and the natamycin-rifampin combination was more effective in fungal killing.

GROUP 3: Amphotericin B and rifampin acted synergistically against 75% of the organisms in this group, amphotericin B and gentamicin against 25%, and both amphotericin B and clindamycin and amphotericin and tetracycline against 12% (Table 6). As before, rifampin was the most effective antibiotic when combined with amphotericin B ($P<.06$). Only when amphotericin B and rifampin were used against *Paecilomyces lilacinus* and *S. brevicaulis* was there no evidence of synergism. Natamycin and rifampin were synergistic against 25% of the strains, and both the natamycin-gentamicin combination and the natamycin-tetracycline combination were synergistic against 12.5%. The effect of combining natamycin and clindamycin against Group 3 organisms was indifferent. Like the synergism between natamycin and the antibiotics against *Fusarium,* their effect on the Group 3 fungi was to reduce the minimal fungicidal concentration, namely, to increase natamycin's ability to kill fungi.

Killing curve studies—A representative killing curve between amphotericin B and rifampin against a strain of *C. albicans* is shown (Table 7). Synergism was demonstrated by a fourfold reduction in both the minimal inhibitory concentration and the minimal fungicidal concentration of combined amphotericin B and 25 μg/ml of rifampin. The curve showed a marked increase in the fungicidal effect of all three concentrations of amphotericin B and at all three times (four, eight, and 24 hours), which satisfied the criteria for synergism as defined by Jawetz.[21] Against the strain of *C. parapsilosis,* synergism was also demonstrated by a greater than two-log decrease in organism counts at eight and 24 hours. There was therefore excellent correlation between the killing curve method and the method used in this study.

DISCUSSION

Synergism between drugs is an effect greater than that of each drug used alone. In strict pharmacologic terms, synergism is generally referred to as an interaction between heterergic drugs, namely, when the effect of one of the drugs is zero.[21,22] An example of this type of interaction occurs when penicillin and probenecid are combined. Probenecid alone has no antibacterial effect, but by delaying the renal excretion of penicillin, it potentiates the action of the penicillin in vivo against susceptible organisms. Combinations of antibiotics are usually homergic, namely,

TABLE 6

DRUG INTERACTIONS AGAINST FILAMENTOUS FUNGAL ISOLATES OTHER THAN *Fusarium**

Drug Combination*	Synergism MIC Only	Synergism MFC Only	Synergism Both MIC and MFC	Total Synergism (%)	Antagonism (%)
AB + R	3/8	0	3/8	75	0
AB + G	1/8	1/8	0	25	0
AB + C	1/8	0	0	12.5	0
AB + T	0	1/8	0	12.5	0
NAT + R	0	2/8	0	25	0
NAT + G	0	1/8	0	12.5	0
NAT + C	0	0	0	0	0
NAT + T	0	1/8	0	12.5	0

*MIC designates minimal inhibitory concentration; MFC, minimal fungicidal concentration.
†AB designates amphotericin B; NAT, natamycin; R, rifampin; G, gentamicin; C, clindamycin; T, tetracycline.

each drug used alone has a finite effect. Because of the difficulty of determining the sum of the effects of two antibiotics, a number of criteria for synergism between antibiotics have been suggested.[21] None is entirely satisfactory, however. At concentrations of 25 μg/ml, the antifungal effect of the antibiotics tested with antifungal drugs in this study was so small (one tenth or less of the minimal inhibitory concentration) as to approach zero. This concentration was chosen because it would be ineffective against most fungi but could usually be achieved in the cornea,[23] and in some cases in the inner eye, by local administration. In this study, therefore, the combinations tested were considered to be heterergic. This meant that any significant decrease in the minimal inhibitory concentration or minimal fungicidal concentration of the antifungal agent in the presence of an antibiotic could be considered synergism.

The mechanisms of this type of synergism have been well established. Polyene antibiotics, such as amphotericin B, bind to sterols, primarily ergosterol, in the fungal cell membrane and increase the membrane's permeability.[24] At therapeutic levels, this increased permeability allows the intracellular ions and other substances to pass through the membrane, and this either inhibits the growth of the organism or kills it. At levels below the level

TABLE 7

QUANTITATIVE KILLING STUDY AGAINST ONE STRAIN OF *Candida albicans*

Drug Combination*	Organisms per ml			
	0 hrs	4 hrs	8 hrs	24 hrs
No drug	1.3×10^5	1.3×10^6	2.1×10^7	1.2×10^{10}
Rifampin 25 μg/ml	1.3×10^5	6.2×10^5	9.25×10^6	6.6×10^9
AB 1.6 μg/ml	1.3×10^5	5.58×10^6	1.75×10^7	6.7×10^9
AB 1.6 μg/ml + rifampin 25 μg/ml	1.3×10^5	$<1 \times 10^2$	$<1 \times 10^2$	$<1 \times 10^2$
AB 0.4 μg/ml	1.3×10^5	1.32×10^6	2.6×10^7	8.7×10^9
AB 0.4 μg/ml + rifampin 25 μg/ml	1.3×10^5	1.65×10^3	$<1 \times 10^2$	$<1 \times 10^2$
AB 0.1 μg/ml	1.3×10^5	6.1×10^6	3.2×10^7	9.75×10^9
AB 0.1 μg/ml + rifampin 25 μg/ml	1.3×10^5	3.28×10^3	5.0×10^2	$<1 \times 10^2$

*AB designates amphotericin B.

that inhibits growth, the permeability of the cell membrane may increase enough to allow the penetration of antibiotics and other antimetabolites that ordinarily have no effect.[6,9,25] The specific effects of the antibiotic, for example, the inhibition of ribonucleic acid synthesis by rifampin, can then be detected within the organism. By means of this mechanism, the polyene antifungal agent is thus potentiated by the antibiotic or antimetabolite.

The study suggests that polyene antifungal agents combined with rifampin, and possibly with other antibiotics in certain cases, may be more effective in treating most ocular fungal infections than a polyene antibiotic alone. The principal effect of the interaction of amphotericin B and rifampin was to reduce the minimal inhibitory concentration of amphotericin B, namely, to increase its fungistatic effect. The value of this interaction would be twofold: (1) organisms not susceptible to amphotericin B alone might be susceptible to the drug combination; and (2) in the treatment of susceptible organisms, the dosage of amphotericin B could be decreased, thereby avoiding toxicity. The second value would be considerably important in the treatment of keratomycosis: although the topical use of high concentrations of amphotericin B is irritating and toxic to the corneal epithelium, low concentrations are relatively well tolerated[26]; and when the systemic administration of amphotericin B is indicated, as in the cases of fungal endophthalmitis and cerebro-rhino-orbital phycomycosis, a potentiation of antifungal action and a reduction in systemic toxicity would both be important.

The effect of the interaction between natamycin and either rifampin or gentamicin was to increase fungal killing. The use of fungicidal rather than fungistatic drugs is desirable in all cases, and is especially important in patients with compromised defense mechanisms. Because most cases of keratomycosis occur in patients whose cell-mediated defenses have been compromised iatrogenically by the use of topical corticosteroids,[27] the enhancement of natamycin's fungicidal effect on *Fusarium* by adding rifampin or gentamicin gives added significance to the natamycin antibiotic combination against *Fusarium* infections.

Although amphotericin B and rifampin were synergistic when used against a wide variety of fungi, and natamycin and rifampin or gentamicin were synergistic when used against *Fusarium*, not all of the polyene-antibiotic combinations were synergistic. Interactions between the polyene antifungal agents and clindamycin were characterized almost exclusively by indifference, and the combination of amphotericin B and tetracycline HCl had an antagonistic effect on a significant percentage (14%) of organisms. Although combinations of amphotericin B and tetracycline HCl have been shown to be less synergistic than amphotericin B and other tetracycline derivatives,[14] antagonism resulting from this combination has not been previously observed. The mechanisms of such antagonism is unclear, but its occurrence suggests that polyene antifungal agents and antibiotics should not be used together indiscriminately until their favorable effects have been demonstrated experimentally. The specific combination of amphotericin B and tetracycline was shown in this study to be potentially harmful.

SUMMARY

A microtiter method for the determination of fungal sensitivities was used to determine the minimal inhibitory and fungicidal concentrations of two antifungal agents, amphotericin B and natamycin, both alone and in combination with four different antibiotics: rifampin, gentamicin, clindamycin, and tetracycline. Synergism was defined as a fourfold or greater reduction in the minimal

inhibitory concentration, minimal fungicidal concentration, or both, of the antifungal agent in the presence of antibiotic; antagonism was defined as fourfold or greater increase in the minimal inhibitory concentration, minimal fungicidal concentration, or both. Amphotericin B and rifampin were synergistic against the majority of organisms, but synergism between amphotericin B and other antibiotics was infrequent. Combinations of natamycin and rifampin or of natamycin and gentamicin were synergistic against the majority of *Fusarium solani* tested. Combinations of amphotericin B and tetracycline were antagonistic against 14% of the organisms.

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CHOROIDAL OSTEOMA

TULLOS O. COSTON, M.D. AND C. P. WILKINSON, M.D.
Oklahoma City, Oklahoma

The characteristics of choroidal osteomas were recently described by Gass.[1] His series consisted of five eyes of four female patients; one eye had been enucleated because of concern that the choroidal lesion was malignant.

We report a case of a choroidal osteoma observed at an earlier stage than the lesions described by Gass. Because of its apparent growth and a positive radioactive phosphorous uptake (^{32}P) test, the tumor closely mimicked an amelanotic choroidal melanoma.

CASE REPORT

A 15-year-old white girl was referred to us for evaluation of a choroidal lesion in the right eye. The patient's medical history was unremarkable. She was hyperopic and gave a history of having strabismus surgery performed on the right eye at age 2 years. In the few months before her referral she had noted slight blurring of central vision in the right eye.

At her initial examination in April 1975, her best corrected visual acuity was R.E.: 6/9 (20/30), and L.E. 6/4.5 (20/15). No changes in her hyperopic refractive error had occurred. Results of intraocular examination of the left eye were within normal limits. In the posterior pole of the right eye we observed an ovoid, reddish-orange, minimally elevated, sharply demarcated choroidal lesion (Fig. 1, top left). Minimal alterations in the retinal pigment epithelium were observed, but no subretinal fluid was detected. Fluorescein angiography performed at this time revealed only minimal changes in the retinal pigment epithelium overlying the choroidal tumor (Figs. 2 and 3). At this time we believed the lesion was a choroidal hemangioma.

The patient returned in October 1975, and we observed increased alteration of the retinal pigment epithelium overlying the lesion (Fig. 1, top right). A fluorescein angiogram obtained at this time documented these changes but demonstrated no circulation within the tumor or leakage from its surface (Figs. 4 and 5). A- and B-scan ultrasonograms obtained at this time demonstrated a mass of high reflectivity 2.5 mm in elevation. We elected to observe the patient; she returned in February 1976 and her visual acuity was the same, but the lesion appeared to have extended temporally (Fig. 1, bottom left). Because of this apparent growth a ^{32}P test was performed, and the counts over the lesion were approximately 350% greater than those over normal portions of the posterior pole. A small amount of subretinal bleeding occurred soon after the study (Fig. 1, bottom left). We strongly considered enucleation of the eye at this time. However, because the apparent growth of this lesion was in a flat area, we thought the changes might be due to increasing pallor in the retinal pigment epithelium at the edge of the lesion. Additionally, an A-scan ultrasonogram showed no apparent growth in the height of the lesion. We therefore continued to examine this patient with serial photography and ultrasonography.

In the following months the lesion continued to change in color, becoming increasingly paler and more yellow, and its apparent size increased. Nevertheless, all sites of possible growth occurred in areas in which the lesion remained flat, and ultrasonograms continued to show no change in the height of the lesion. Visual acuity returned to 6/6 (20/20) by October 1976. In April 1977, after we heard J. Donald M. Gass, M.D., describe choroidal osteomas, a computed axial tomography scan was obtained. This revealed dense calcification in the choroid of the right eye (Fig. 6). In June 1977 visual acuity was 6/6 (20/20)–2. The lesion has continued to evolve into a picture more characteristic of the lesions described by Gass (Fig. 1, bottom right). Subsequent plain orbital x-rays have demonstrated calcium in the back of the right eye.

DISCUSSION

Osteomas previously have been reported in the epibulbar structures of otherwise normal eyes[2] and in old atrophic globes.[3] Gass recently published the original description of osteomas of the choroid, and in his presentation the typical clinical, histological, angiographic, ultrasonographic, and radiographic features of these lesions were thoroughly discussed. Ours is the sixth case of choroidal osteoma to be reported; it is important because it was observed before the lesion exhibited the clinical characteristics described by Gass. It therefore provides some clues

From the Dean A. McGee Eye Institute and Department of Ophthalmology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma.

Reprint requests to Tullos O. Coston, M.D., Dean A. McGee Eye Institute, 608 Stanton L. Young Dr., Oklahoma City, OK 73104.

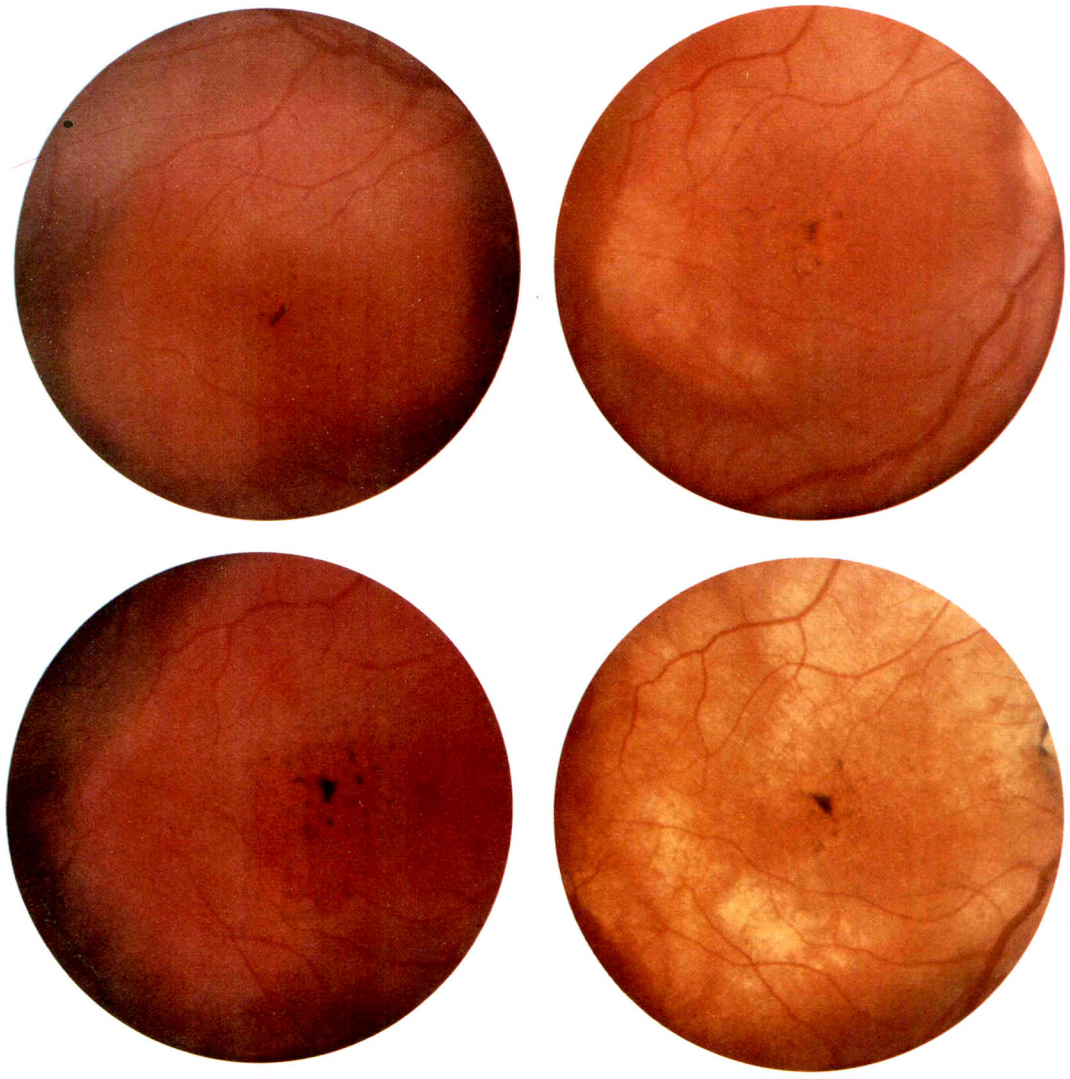


Fig. 1 (Coston and Wilkinson). Fundus photographs of changes in the lesion in the right eye. Top left, The patient's initial visit in April 1975. Top right, October 1975. There are more pigment epithelial changes. The apparent color change in the temporal portion of the lesion is largely a photographic artifact. Bottom left, February 1976. The tumor appears to have extended temporally. A small amount of subretinal bleeding occurred at the time of the positive ^{32}P test. Bottom right, June 1977. The tumor is larger and paler than in previous photographs.

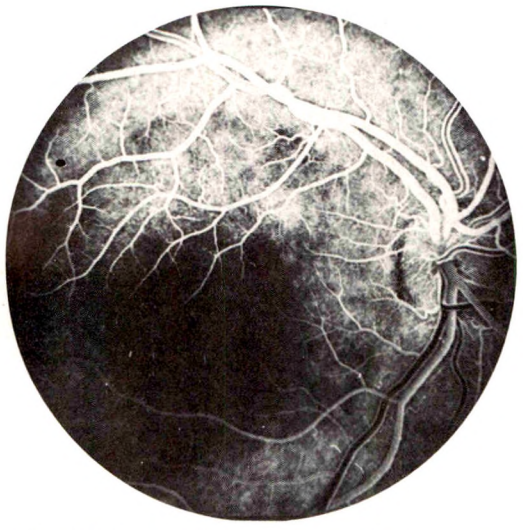


Fig. 2 (Coston and Wilkinson). Early stage of the fluorescein angiogram performed in April 1975. Only minimal pigment epithelial defects are present.

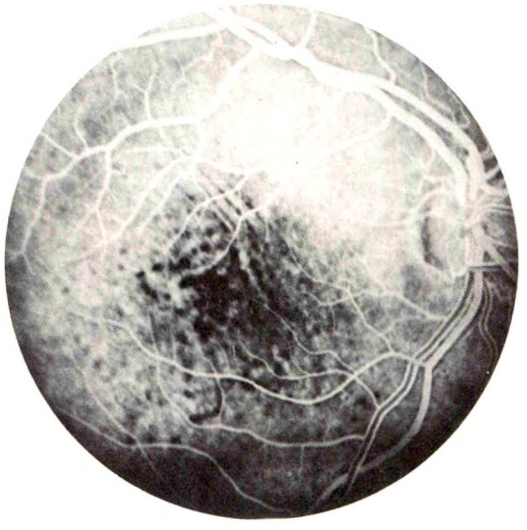


Fig. 4 (Coston and Wilkinson). Early stage of the fluorescein angiogram performed in October 1975. More significant changes in the retinal pigment epithelium are evident.

about the origin of the lesion. In the past, tumors such as these have been thought to represent osseous metaplasia occurring within a cavernous hemangioma.[3] Although some osseous metaplasia occurs in 20% of choroidal hemangiomas,[4] the extent of these changes tends to correlate with the duration of the lesion and with significant changes in the overlying retinal pigment epithelium and sensory reti-

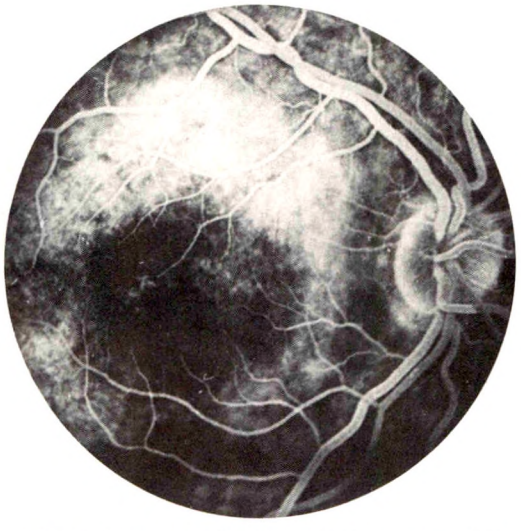


Fig. 3 (Coston and Wilkinson). Late stage of the initial angiogram. Staining is present in the superior portion of the tumor.

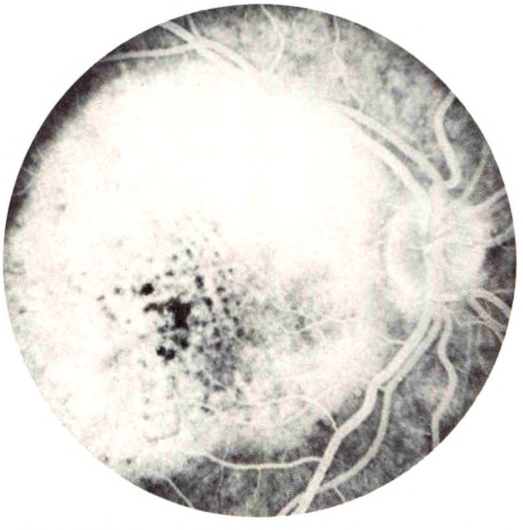


Fig. 5 (Coston and Wilkinson). Late stage of the angiogram of October 1975. Although there is increased staining of the lesion, neither tumor circulation nor leakage are present.

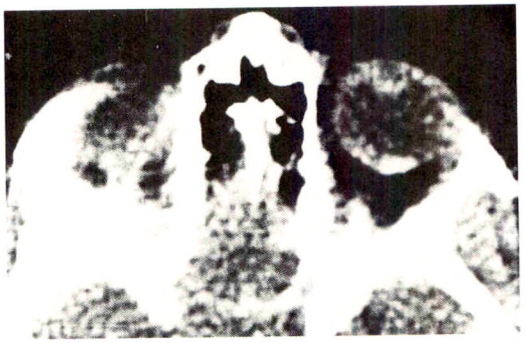


Fig. 6 (Coston and Wilkinson). Computed axial tomography scan of the patient's right eye. Dense calcification is present in the posterior pole.

na. The tumor in our patient was apparently an "early" lesion over which minimal pigment epithelial changes had taken place. Although these changes have progressed somewhat in the 30 months since she was first observed, they remain modest with little evidence of pigment epithelial hyperplasia, and visual acuity is 6/6 (20/20) in the eye. These factors favor the lesion being a primary osteoma of the choroid rather than osseous metaplasia associated with a cavernous hemangioma or heterotopic ossification related to inflamation or trauma.

Our initial impression of choroidal hemangioma was altered when the tumor appeared to grow. When the ^{32}P test was performed, we became increasingly concerned about the possibility of an amelanotic melanoma or metastatic carcinoma. In retrospect, this apparent growth may well have been only change in the retinal pigment epithelium or the color of the tumor, as no increases in the height of the lesion were observed clinically or on serial ultrasonograms. This lack of growth is consistent with the hypothesis that these tumors are choristomas.

Choroidal osteomas must be considered in the differential diagnosis of amelanotic choroidal tumors, particularly if they occur in the posterior pole. The recognition of these lesions is particularly important since they cause a positive ^{32}P test.

Summary

A 15-year-old white girl had a presumed choroidal hemangioma in the posterior pole of the right eye. The lesion appeared to grow, and we performed a phosphorous uptake test, which was positive. Subsequent studies demonstrated that the tumor was a choroidal osteoma.

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RHEGMATOGENOUS RETINAL DETACHMENT FOLLOWING CHORIORETINAL INFLAMMATORY DISEASE

WILLIAM S. HAGLER, M.D., WILLIAM H. JARRETT II, M.D.,
AND
MEIMEI CHANG, M.D.
Atlanta, Georgia

Acute or chronic chorioretinal inflammatory disease may have associated retinal tears and detachments. This has been well documented in patients with toxoplasmic chorioretinitis[1–6] and has been described in patients with *Toxocara canis* and other forms of uveitis.[7–9]

We report herein the incidence of retinal detachment associated with preexisting active or inactive chorioretinal inflammatory disease in a large series of unselected patients operated on during the past seven years. We compared the major clinical features and behavior of this group of postinflammatory rhegmatogenous retinal detachments with those of another group of patients whose detachments were not associated with prior ocular inflammatory disease.

MATERIAL AND METHODS

Between Jan. 1, 1970, and Dec. 31, 1977, 2,618 eyes were operated on for retinal detachment. This was determined by a previously described retrospective computerized chart retrieval method.[10] Forty-four cases (1.7%) had evidence of posterior or generalized uveitis. Of these 44 cases, five had bilateral uveitis without detachment. Various factors were identified and compared in these two groups using the chi-square test for determining statistical significance ($P < .05$).

This study included only those patients on whom retinal detachment surgery was performed. There was no method of recalling patients with retinal detachment and chorioretinitis on whom no operation was performed. Thus, we can make no statement regarding the percentage of patients with various types of chorioretinitis who eventually developed retinal detachment. The patients who had a rhegmatogenous retinal detachment associated with the syndrome of massive choroidal detachment, uveitis, and hypotony were not included because the panuveitis was thought to be the consequence and not the cause of their retinal detachment.

All patients had a complete ophthalmologic examination on admission to the hospital. This included a detailed fundus drawing using the stereoscopic indirect ophthalmoscope with scleral depression, and slit-lamp biomicroscopy of the anterior and posterior segments using the three-mirror Goldmann lens. B-scan ultrasonography was performed in patients whose media were so opaque that the retina could not be seen adequately.

All patients underwent a preoperative medical examination. An all inclusive uveitis survey was not attempted. Serologic testing was based primarily on our clinical impression as to the possible etiology of the uveitis. Many patients had undergone previous serologic testing by their referring ophthalmologists, and these tests were generally not repeated.

RESULTS

Incidence—During this seven-year interval, 44 cases (1.7%) had a retinal detachment caused by an active or inactive chorioretinitis. The incidence of postinflammatory detachments for each year varied from 1.1% to 3.1%, but these yearly

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Reprint requests to William S. Hagler, M.D., 2004 Peachtree Rd., N.W., Atlanta, GA 30309.

differences were not statistically significant.

Sex and race—There was no difference between the postinflammatory detachments and the noninflammatory detachments with respect to sex and race. Our data confirm the findings of others[11,12] that retinal detachment occurs more commonly in whites than in blacks (Table 1).

Age—The incidence of retinal detachment in the postinflammatory group was greatest in the earlier decades (60% occurred in patients under 40 years of age), whereas in the noninflammatory group, the incidence of detachment was greatest in the later decades (79% of patients over 40 years of age) (Table 2).

Status of lens—In the postinflammatory group, 14% were aphakic, whereas in the noninflammatory group, 45% were aphakic. This is statistically significant at P=.005 and may be related to the younger age distribution of the patients with postinflammatory detachment (Table 3).

Duration of detachment—The postinflammatory group had a significantly longer estimated duration of the detachment at the time of diagnosis (119 days, as compared with 43 days for the noninflammatory group). This difference is statistically significant. Furthermore, only 42% of the detachments in the postinflammatory group were diagnosed within two weeks, as compared to 60% of the detachments of the patients in the noninflammatory group.

Number of retinal breaks—The number of retinal breaks present was tabulated (Table 4). The majority of patients in both groups had two tears or less. However, 19% of the noninflamed eyes had four breaks or more, as compared with 11% of the inflamed eyes. This was a statistically significant difference.

In six eyes (14%) in the postinflammatory group, a definite retinal tear could not be identified. However, there were other features characteristic of rhegmatogenous detachment in these cases,

TABLE 1

SEX AND RACE CORRELATIONS

	Non-Pird* (%)	Pird† (%)
Male	41	59
Female	59	41
White	95	93
Black	4.6	7

*Non-Pird designates non-postinflammatory retinal detachment group.

†Pird designates postinflammatory retinal detachment group.

TABLE 2

AGE DISTRIBUTION

Age (yrs)	Non-Pird* (%)	Pird† (%)
1-10	2	4.5
11-20	7	21
21-30	7	23
31-40	5	11
41-50	10	11
51-60	25	14
61-70	28	11
Over 70	16	4.5

*Non-Pird designates non-postinflammatory retinal detachment group.

†Pird designates postinflammatory retinal detachment group.

TABLE 3

LENS STATUS

Status	Non-Pird* (%)	Pird† (%)
Phakic	55	86
Aphakic	45	14

*Non-Pird designates non-postinflammatory retinal detachment group.

†Pird designates postinflammatory retinal detachment group.

TABLE 4

NUMBER OF BREAKS

No. of Breaks	Non-Pird* (%)	Pird† (%)
0	2	14
1	43	34
2	24	30
3	12	11
4	6	9
5-10	11	2
>10	2	0

*Non-Pird designates non-postinflammatory retinal detachment group.

†Pird designates postinflammatory retinal detachment group.

and we believe that a tear was indeed present, but simply could not be seen because of opacification of the media. In the noninflamed group, breaks were not seen in only 2% of the cases.

Vitreous membranes—Ophthalmoscopically visible vitreous membranes were noted in 72% of the postinflammatory group and only 19% of the noninflammatory group. This was again significant at P=.005 (Table 5).

Folds—Fixed folds, either equatorial, meridional, or star-shaped, were present in roughly the same percentage in both groups of patients and occurred in 18% of the inflammatory group and in 17% of the noninflammatory group.

TABLE 5

VITREOUS PATHOLOGY

Status	Non-Pird* (%)	Pird† (%)
No disease	22	9
Peripheral vascular disease	59	19
Vitreous membranes	19	72

*Non-Pird designates non-postinflammatory retinal detachment group.

†Pird designates postinflammatory retinal detachment group.

Status of macula—The macula was detached during diagnosis in approximately the same incidence: 68% of the noninflammatory group and 70% of the postinflammatory group. Preoperative macular puckers occurred in 2.3% of the noninflammatory group and in 7% of the inflammatory group, which was statistically significant.

Status of the ciliary epithelium—The ciliary epithelium was attached in approximately 80% of both groups, detached in less than one quadrant in 10%, and greater than one quadrant in 10%, essentially the same in both groups. A traumatic avulsion was recorded in 1% of the noninflammatory group.

Etiology of the uveitis—The underlying causes of the inflammatory disease were classified as follows: toxoplasmosis, 36%; pars planitis, 25%; and ocular toxocariasis, 7%. In 32% of the eyes no cause could be established.

The uveitis was active when the retinal detachment was diagnosed in 48% of these cases. Half of these had both an anterior and posterior involvement, whereas the other half had only a posterior uveitis.

Surgical procedures—The various types of surgical procedures used in repairing these detachments are classified (Table 6). Cryocoagulation was used exclusively to achieve chorioretinal scarring around the retinal tears. Generally, most of the eyes had an encircling procedure using an encircling silicone exoplant. If a localized exoplant was used, this was usually solid molded silicone, and in only a few instances was a silicone sponge used. These were sutured to intact sclera; scleral undermining was not performed in any case. In selected cases intravitreal air or gas (SF-6) injections were used either alone or in conjunction with a buckling procedure. Closed pars plana

TABLE 6

SURGICAL PROCEDURE*

Type of Surgery	No. of Non-Pirds†	No. of Pirds‡
Transconjunctival cryocoagulation	199	4
Transscleral cryocoagulation	223	4
Segmental silicone with cryocoagulation	250	1
Circling silicone with cryocoagulation	2,057	38
Buckle with miscellaneous	22	2

*Patients requiring reoperation: non-Pird group, 556; Pird group, 5.

†Non-Pird designates non-postinflammatory retinal detachment group.

‡Pird designates postinflammatory retinal detachment group.

vitrectomy was performed in only two cases in the postinflammatory group: in one, to clear significant vitreous membranes; in the other, following a scleral buckling procedure to sever vitreous traction bands that had caused a redetachment.

Anatomical reattachment was obtained in 92% of the noninflammatory detachment group and in 91% of the postinflammatory detachment group, based on a minimum of a six-month to a one-year follow-up.

Visual results—The visual results were tabulated in those patients on whom an anatomical reattachment was achieved and on whom sufficient follow-up data were available (Tables 7 and 8). In both groups the majority of patients achieved improvement in postoperative visual acuity (68% of the noninflammatory group vs 57% of the postinflammatory group). In 9% of the noninflammatory group, some loss of vision occurred after a successful reattachment operation, as compared with 14% in the postinflammatory group. However, this was not a statistically significant difference.

TABLE 7

VISUAL ACUITY IN NON-POSTINFLAMMATORY DETACHMENT GROUP*

Final Visual Acuity	No. of Eyes	Percent
Improved	1,498	68
No change	520	23
Decreased	187	9

*Total number of eyes in group is 2,195.

Complications—There was no statistically significant difference in the major operative and postoperative complications between the inflamed and noninflamed eyes (Table 9).

DISCUSSION

Toxoplasmosis, pars planitis, and ocular toxocariasis accounted for 68% of retinal detachment caused by chorioretinal inflammatory disease in our series of patients. In the remaining 32% a variety of other disorders caused significant vitreous inflammation for which no etiology could be determined.

The diagnosis of toxoplasmosis is established by the typical clinical findings of an acute retinochoroiditis with overly-

TABLE 8

VISUAL ACUITY IN POSTINFLAMMATORY DETACHMENT GROUP*

Final Visual Acuity	No. of Eyes	Percent
Improved	28	57
No change	14	29
Decreased	7	14

*Total number of eyes in group is 49.

TABLE 9

SURGICAL COMPLICATIONS

Complication	Non-Pirds*		Pirds†	
	No.	Percent	No.	Percent
Choroidal hemorrhage	72	7	2	4.5
Choroidal detachment	286	29	6	13.6
Retina incarcerated	36	4	—	
Subretinal hemorrhage	156	16	3	6.8
Hyphema	13	1	—	
Vitreous hemorrhage	29	3	1	2.3
Iatrogenic hole	9	0.9	—	
Fish mouth	35	4	1	2.3
Vitreous loss	16	2	1	2.3
Severe uveitis	13	1	1	2.3
Early infection	6	0.6	—	
Late infection	12	1	—	
Granuloma	12	1	—	
Endophthalmitis	3	0.3	—	
Wound dehiscence	2	0.2	1	2.3
Corneal changes	10	1	1	2.3
Glaucoma	37	4	—	
Cataract	12	1	2	4.5
Macular pucker	56	2.3	4	9.0
Massive vitreous retraction	70	7	1	2.3
Vitreous membranes	47	5	2	4.5
Extrusion of implant	5	0.5	—	
Intrusion of implant	3	0.3	—	
Total	940	36.8	26	59.1

*Non-Pird designates non-postinflammatory retinal detachment group.
†Pird designates postinflammatory retinal detachment group.

ing vitreous reaction in the acute stage or an old chorioretinal scar in the chronic or inactive phase. A positive Sabin-Feldman dye titer provides confirmation of the diagnosis in most cases. Cases of pars planitis are recognized by the typical "snow bank" appearance over the inferior pars plana, along with signs of perivasculitis and a minimal to moderate vitritis.

Nematode endophthalmitis caused by the larva of *T. canis* has only recently been recognized and diagnosed by ophthalmologists. Ashton[13] first described the pathologic features of this disease, and Welch and Wilkinson[14,15] described its clinical manifestations. In our cases of ocular toxocariasis with retinal detachment, the chorioretinitis was most often located peripherally and in the upper nasal or temporal quadrants.

Until recently the diagnosis of ocular toxocariasis remained a purely clinical one because there were no reliable laboratory tests for this condition. The recently developed enzyme-linked immunosorbent assay test is now being studied and appears to afford a reasonably reliable serologic test for this disease.[16]

Although we failed to identify any such cases in our series, a variety of viral infections have been found to involve the retina and can lead to a retinal detachment.[2,5,6,17,18] Specifically included in this group are the cytomegalovirus infections in the newborn and in immunosuppressed adults[19] and the viruses of herpes

simplex and varicella zoster. This may become more important to the retinal surgeon as irradiation and chemotherapy are used more extensively in treating various forms of cancer.

It is sometimes extremely difficult to perform an adequate fundus examination in patients with ocular inflammation. Vitreous haze, vitreous membranes, and complicated cataracts make visualization of the retina and retinal tears more difficult than in patients without inflammatory disease.

In patients with retinal detachment in whom a retinal tear cannot be found, it is difficult to determine whether the patient has a secondary inflammatory retinal detachment or a rhegmatogenous detachment caused by a tear that simply cannot be seen. The presence of shifting fluid, choroidal detachment, and the absence of starfolds are clinical features of exudative retinal detachment, and these signs are frequently helpful in identifying such cases and avoiding unwarranted detachment surgery.

In this series of 44 patients, we considered the detachment to be caused by a retinal tear, and the patients were treated by various types of surgical procedures. Typically, the inflammatory group had fewer retinal tears than the noninflammatory group. The majority of the former had only one or two breaks that characteristically occurred in one of two locations: directly over or immediately adjacent to a large chorioretinal focus, either active or inactive, or approximately 180 degrees away from a chorioretinal inflammatory focus at the end of a vitreous traction band.

The majority of the retinal tears in our series were horseshoe in configuration. Round or oval holes were rarely present (five eyes), and in those instances, they occurred in the middle of firm vitreoretinal traction bands. Giant tears were noted in only two eyes in which the uveitis was of two and three years' duration, presumably a result of chronic vitreous membrane contraction. There were no eyes in which peripheral retinal degenerations (for example, lattice degeneration) or occlusive vascular disorders appeared to play a causative role in retinal tear formation with subsequent retinal detachment. These findings appear to support the role of vitreoretinal traction as the major cause of retinal tear formation in our series of patients with postinflammatory retinal detachments.

Half of our patients who had a detachment related to inflammatory disease had an active inflammation during their first examination. The presence of active uveitis is a complicating factor, and the surgeon must use judgment in deciding whether or not medical treatment for the uveitis should be instituted before or with retinal detachment surgery.

In certain cases of acquired ocular toxoplasmosis, the proper use of systemic or periocular corticosteroids alone to clear the uveitis can have a devastating effect.[20–22] Therefore, the decision to use corticosteroids with or without antibiotics must be carefully considered.

If the vitreous is so hazy that adequate localization of retinal tears cannot be performed, then the surgeon must decide whether and when to perform a surgical vitrectomy before or with a buckling procedure. This can be helpful both to clear the media and to remove dense vitreous membranes. However, in some detachments where the macula is not immediately threatened, it would be advisable to wait a considerable period of time to see if the media could be cleared medically, whereas in other cases more rapid intervention would be indicated to save or preserve some macular vision.

Summary

Preexisting ocular inflammatory disease was responsible for 44 cases (1.7%)

of rhegmatogenous retinal detachment in a large series of consecutive retinal detachments.

Characteristics of retinal detachments following ocular inflammatory disease include a longer duration of the detachment, fewer observable retinal breaks, a higher incidence of visible vitreous membranes and preoperative macular puckers, a younger age distribution, and a higher incidence of phakic patients.

In comparing the group of postinflammatory rhegmatogenous retinal detachments with detachments not associated with inflammation, the following characteristics did not show any statistically significant difference: sex, the eye involved, the status of the ciliary epithelium, the presence or types of retinal folds, the rate of operative complications, or the rate of reattachment at six months.

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CHOROIDAL FOLDS

FRANCIS E. CANGEMI, M.D.
Newark, New Jersey
CLEMENT L. TREMPE, M.D.
Boston, Massachusetts
AND
JOSEPH B. WALSH, M.D.
Bronx, New York

Choroidal folds are lines, grooves, or striae of the posterior pole. They are often arranged in a parallel and horizontal fashion but may be vertical, oblique, or irregular. They appear as a series of light and dark lines, often temporal, confined to the posterior pole, and rarely, if ever, extending beyond the equator.[1,2]

Choroidal folds were first described clinically by Nettleship[3] in 1884. For years this fundus picture was considered a characteristic, although uncommon feature of expanding tumors of the orbit.[4,5] Yet a review of previous studies shows that they had been described in hypotony as well as in endocrine exophthalmos.[6–8]

A major advance in the understanding of this condition occurred in 1968 when Norton[9] described a condition he called "choroidal folds." For the first time the typical fluorescein angiographic appearance of this condition was described, and a clear distinction was made between choroidal and retinal folds. He also demonstrated that a variety of orbital as well as ocular conditions could be associated with this picture. Kroll and Norton[10] described the regression of choroidal folds when the underlying cause was treated.

Newell[1] reviewed 16 cases in his series of choroidal folds: eight cases attributed to orbital causes and eight to a variety of ocular diseases including thyroid disease, hypotony, hyperopia, papilledema, disciform degeneration, and uveitis. Hyvarinen and Walsh[11] reported three cases of choroidal folds associated with inflammation of the orbit or paranasal sinuses. Choroidal folds have also been described in flat hemangiomas of the choroid and ocular hypotony.[12–14]

The importance of fluorescein angiography, particularly in the recognition of choroidal folds as well as the differential diagnosis, has been emphasized in several of the above mentioned references and others.[15,16] A recent review describes the B-sector scan ultrasonography appearance of benign choroidal folds.[17]

We describe herein our findings in 53 patients with choroidal folds, the differential diagnosis, a variety of associated ocular and medical conditions, and possible mechanisms for the development of choroidal folds.

SUBJECTS AND METHODS

The patients for our study came from a review of cases from two large retinal centers, namely, the Retina Associates of Boston, Massachusetts, and the Retina Service of Montefiore Hospital, Bronx, New York. Through a careful review of case records, fundus photographs, and fluorescein angiography studies, 53 patients were documented to have choroidal folds. Because six of these cases were bilateral, the total number of eyes was 59.

From the Retina Service, Eye Institute of New Jersey and New Jersey Medical School-CMDNJ (Dr. Cangemi), Newark, New Jersey; the Retina Associates (Dr. Trempe), Boston, Massachusetts; and the Retina Service, Montefiore Hospital and Medical Center (Dr. Walsh), Bronx, New York.

Reprint requests to Francis E. Cangemi, M.D., Retina Service, Eye Institute of New Jersey, 15 S. Ninth St., Newark, NJ 07107.

The male:female ratio was 34:19. The youngest patient was 11 years old, the oldest was 78 years old, and the median age was 53 years.

Ocular examination included the anterior and posterior segments. Refraction was recorded in all but four eyes. Visual field examination, including central and peripheral fields, as well as Amsler grid studies, was done where possible. Additional tests included Hertel exophthalmometry, color vision testing, appropriate x-ray film studies, computed axial tomography scan, and electrophysiologic studies when indicated. Fluorescein angiography was performed in all but two cases. A careful medical examination was included where possible.

RESULTS

Our data were analyzed from the standpoint of the initial complaint of the patients, 25 of whom had some visual disturbance (Table 1).

Twenty-three (39%) of the 59 eyes had a visual acuity of 6/12 (20/40) or better. Twelve eyes (20%) had a visual acuity of 6/60 (20/200) or less (Table 2).

Fifty-five of the 59 eyes in this study had the refraction recorded on the charts. Of these 55 eyes, 22 (40%) were hyperopic, 13 of which required greater than 3 prism diopters of correction. Three of the bilateral cases were hyperopic. Emmetropia was the next largest category with 18 eyes (33%). Aphakia was present in nine eyes (16%) and myopia in six eyes (11%).

TABLE 1

OCULAR SIGNS OR SYMPTOMS OF CHOROIDAL FOLDS

Complaint	No. of Cases	Total (%)
Progressive loss of vision	25	42
Trauma	11	18
No ocular complaints	11	18
Proptosis	5	9
Pain	2	3
Diplopia	1	2
Sinusitis	1	2
Photopsia	1	2
Presbyopia	1	2
Photophobia	1	2
Total	59	100

TABLE 2

VISUAL ACUITY

Visual Acuity	No. of Eyes	Total (%)
6/6 - 6/12 (20/20 - 20/40)	23	39
6/12 - 6/21 (20/40 - 20/70)	13	22
6/21 - 6/60 (20/70 - 20/200)	11	19
6/60 or less (20/200 or less)	12	20
Total	59	100

Fifteen categories with several subdivisions were listed as probable causes of choroidal folds (Table 3). In several instances, for lack of a definitive diagnosis, several diseases were listed as possible causes. In ten cases no diagnosis could be established.

Fluorescein angiography, the most important tool in the diagnosis of choroidal folds, was performed in all but two cases in our series.

Of the different ocular conditions present in addition to the choroidal folds, preretinal gliosis was the most frequently observed (Table 4).

Most of our patients had had careful medical examinations, and some of the conditions associated with choroidal folds are listed (Table 5). Because the median age in our series was 53 years, the number of cases of arteriosclerosis, hypertension, and diabetes was not thought to be significant.

DISCUSSION

Ophthalmoscopically, choroidal folds appear as a series of alternating light and

TABLE 3

PRESUMED ETIOLOGY OF CHOROIDAL FOLDS

Diagnosis	No. of Eyes
Hypermetropia	9
Macular degeneration	8
Association with retinal detachment	7
Prescleral buckle (1)	
Postscleral buckle (6)	
Hypotony	7
Postcataract surgery (5)	
Postglaucoma surgery (2)	
Trauma	6
Orbital tumors	5
Hemangioma (2)	
Pseudotumor (2)	
Brown's tumor (1)	
Thyroid disease	5
Scleritis	3
Uveitis	3
Ocular tumor	1
Sinusitis	1
Choroiditis	1
Uveal effusion	1
Venous occlusion	1
Papillitis	1
Unknown	10

dark lines in the posterior pole and rarely, if ever, extend beyod the equator. Although they are most often horizontal (Fig. 1) they may be vertical, oblique, or irregular (Fig. 2).

The diagnosis is made mainly by fluorescein angiography, wherein the folds appear as a series of alternating hyperfluorescent and hypofluorescent streaks,

TABLE 4

ASSOCIATED OCULAR FINDINGS IN CHOROIDAL FOLDS

Condition	No. of Cases
Preretinal gliosis	7
Irvine-Gass syndrome	3
Tilted optic disk	1
Uveal effusion	1
Central retinal artery occlusion	1
Retinal venous occlusion	1
Total	14

TABLE 5

ASSOCIATED MEDICAL CONDITIONS IN CHOROIDAL FOLDS

Condition	No. of Cases
Arteriosclerosis	13
Hypertension	11
Diabetes	4
Cancer (nonorbital)	3
Total	31

starting early in the arteriovenous phase, persisting through the late venous phase, and not leaking in the late films (Figs. 3-6). The hyperfluorescent areas correspond to the peaks of the choroidal folds, and the hypofluorescent areas to the valleys. Histopathologic examination of tissues from an eye with a choroidal melanoma and choroidal folds suggested that the hypofluorescent streaks might be explained on the basis of an inclination of the retinal pigment epithelium in the valleys of the folds, causing an increase in the thickness of the retinal pigment epithelium and thus blocking the underlying choroidal fluorescence. The hyperfluores-

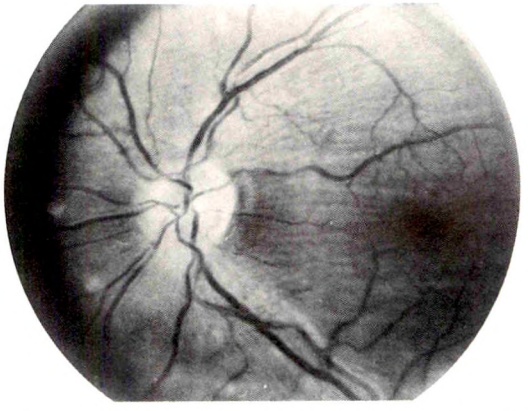


Fig. 1 (Cangemi, Trempe, and Walsh). Typical ophthalmoscopic appearance of alternating horizontal light and dark lines in a 35-year-old woman with choroidal folds. Surgical exploration revealed an orbital hemangioma.

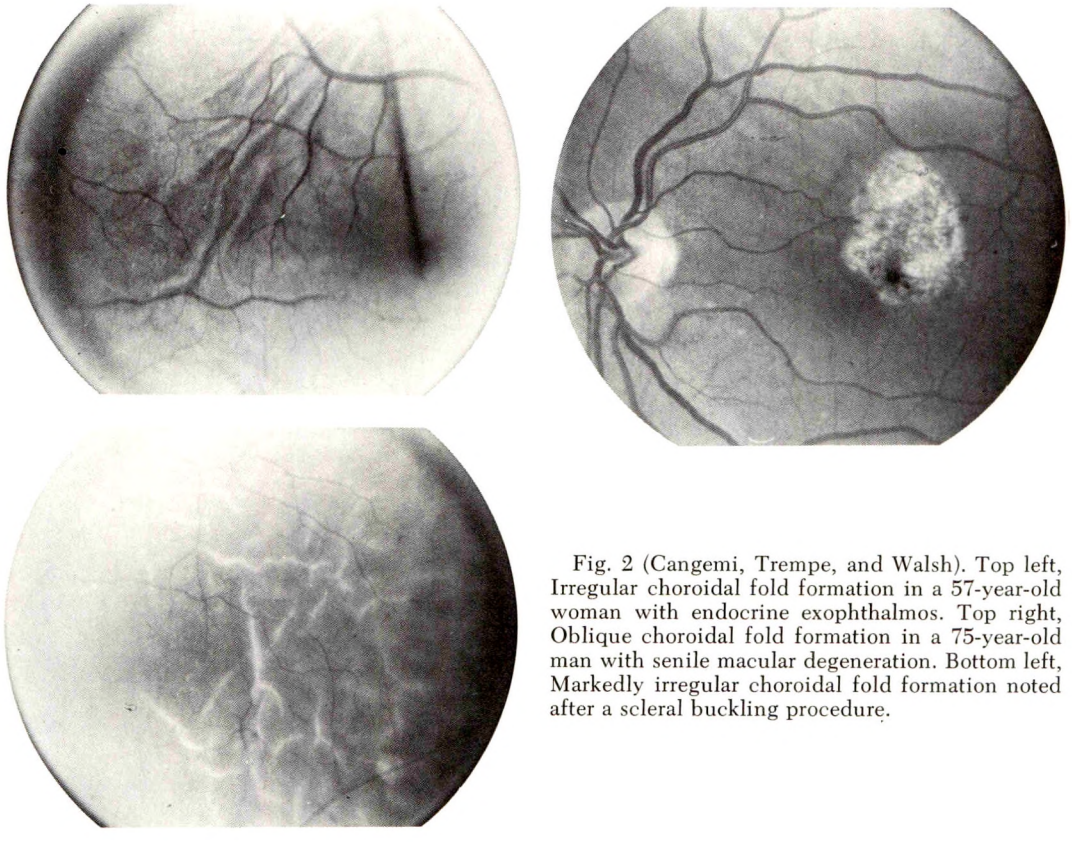


Fig. 2 (Cangemi, Trempe, and Walsh). Top left, Irregular choroidal fold formation in a 57-year-old woman with endocrine exophthalmos. Top right, Oblique choroidal fold formation in a 75-year-old man with senile macular degeneration. Bottom left, Markedly irregular choroidal fold formation noted after a scleral buckling procedure.

cent streaks might be the result of atrophy or thinning of the retinal pigment epithelium over the peaks of the choroidal folds.[9,10,14] Another possible explanation for the fluorescein appearance could be the direct involvement of the choriocapillaris in the valleys of the folds. Any process that could cause a partial collapse of adjacent blood vessels in the choriocapillaris would lead to bands of decreased fluorescein filling in these areas. This corresponds to the valleys of the choroidal folds.[18]

Pathologic studies to date are few. Wolter[19] reported two cases of choroidal folds in eyes removed because of orbital tumors and described the following pathologic changes: (1) internal limiting membrane folds, (2) Bruch's membrane folds, and (3) brain-like corrugations of the retina. Kroll and Norton[10] were able to demonstrate choroidal folds in eyes enucleated after scleral laceration with suprachoroidal hemorrhage, choroidal congestion, and choroidal edema. Wolter[18] later presented histologic evidence confirming the previously stated conclusions of Kroll and Norton.[9,10] He agreed that choroidal folds might best be termed "Bruch's membrane folds" and that the valleys of the folds could be explained by a change in the tension of Bruch's membrane. The involvement of the pigment epithelium was secondary. Three factors could explain the folds in Bruch's membrane: (1) shortening of the posterior sclera because of pressure, (2) papilledema, and (3) congestion causing diffuse thickening of the

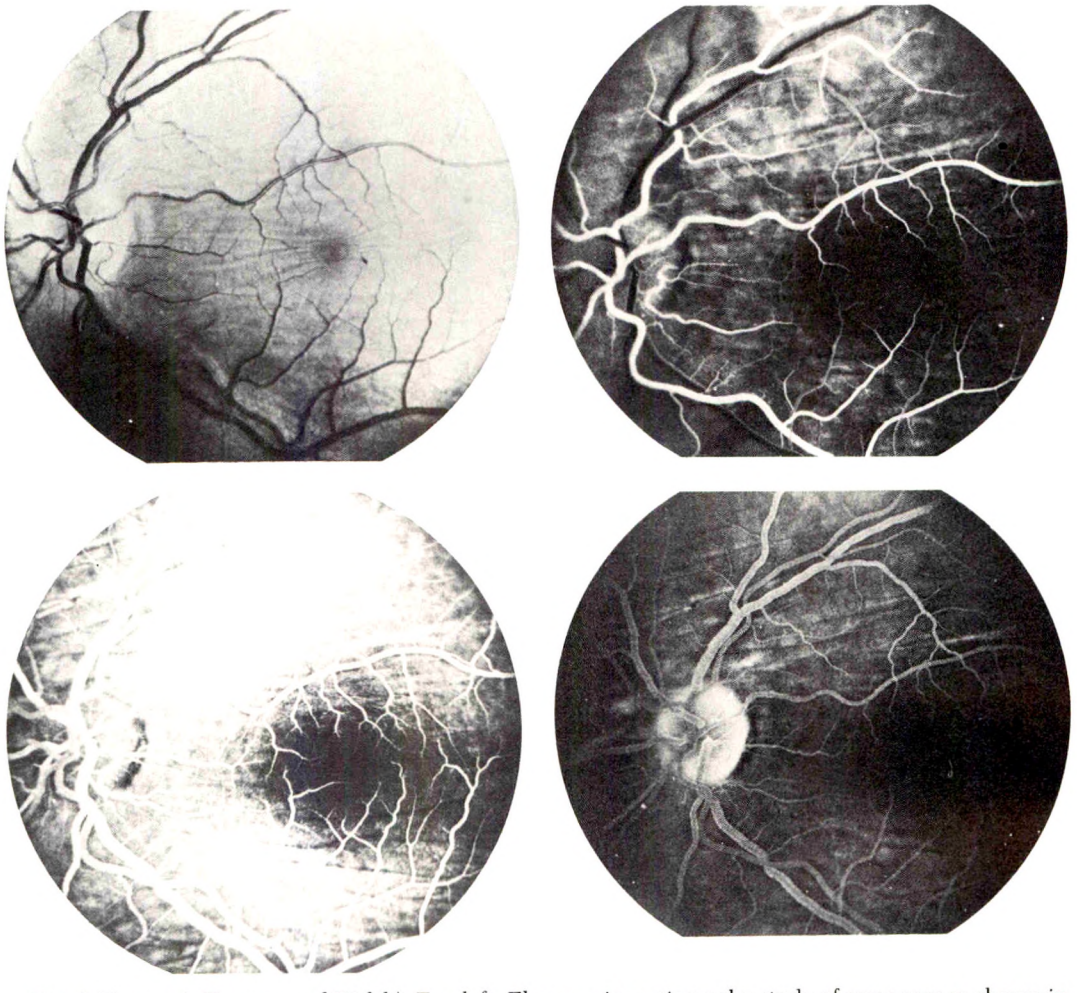


Fig. 3 (Cangemi, Trempe, and Walsh). Top left, Fluorescein angiography study of same case as shown in Figure 1. Just before the beginning of the arterial phase, the alternating light and dark lines can be seen. Note the stellate appearance of the macular region, which probably represents some retinal fold formation. Top right, At the beginning of the venous phase, the alternating hyperfluorescent and hypofluorescent streaks, corresponding to the peaks and valleys of the choroidal folds, can be seen. Bottom left, The streaks are more easily seen in the midvenous phase. Note that the macular region appears uninvolved. Bottom right, In the late stage, there is no leakage of dye.

choroid. Bullock and Egbert[2] produced excellent experimental data in which they hypothesized that choroidal folds could be produced by any mechanism that forced Bruch's membrane to fold and that traction on the optic nerve played a role in the characteristic orientation of the folds.

Choroidal folds thus apparently involve folds of Bruch's membrane and the retinal pigment epithelium and are not related to folds occurring in the inner limiting membrane of the retina or retinal folds. Newell[1] emphasized the importance of recognizing choroidal folds by the fluorescein pattern, particularly with respect to the differentiation of choroidal folds from retinal folds,[20,21] which ophthalmoscopically appear somewhat finer,

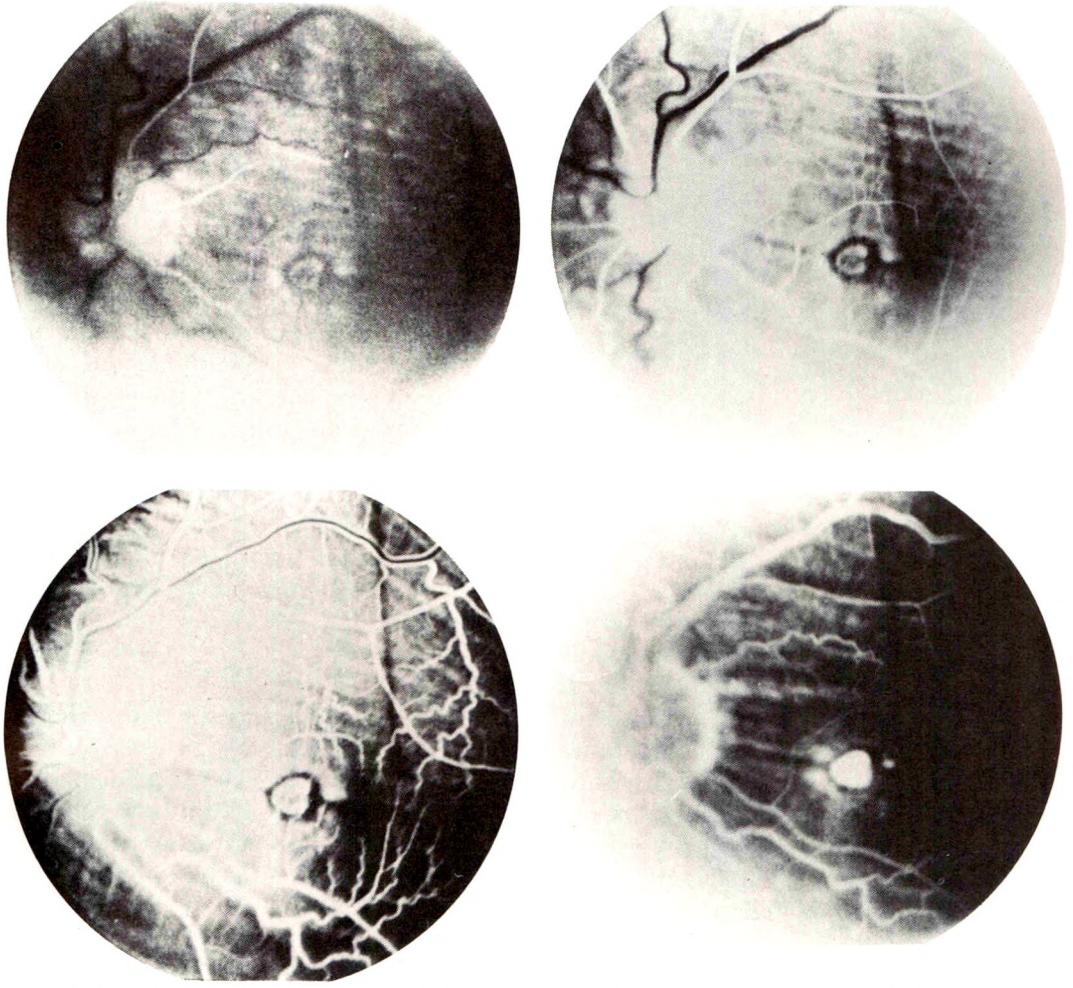


Fig. 4 (Cangemi, Trempe, and Walsh). Top left, In a case of fungal choroiditis in the arterial phase, alternating hyperfluorescent and hypofluorescent streaks are seen. Additionally, there are scattered retinal pigment epithelium defects as well as evidence of subretinal neovascularization in the foveal region. Top right, Later stage of same case in which the streaks appear more prominently. Bottom left, In the venous phase the streaks stand out clearly. Additionally, there is some blurring of the temporal disk margin. Bottom right, Late films show intense staining in the foveal region, as well as several scattered retinal pigment epithelium defects. No leakage is seen around the choroidal folds.

are often associated with vitreous disease, and have a normal fluorescein pattern (Fig. 7).

Initially, choroidal folds were considered a sign of an expanding orbital tumor, and Reese[4] thought that the location of the folds indicated the point at which the tumor indented the globe. Subsequent works have not only shown a variety of causes, but also that the location of the folds is not related to the tumor compressive factor.[1,8,9–16]

Our series represents the largest series of choroidal folds reported to date (Table 3). We present a variety of possible causes in the formation of choroidal folds. Our cases showed a relative scarcity of orbital causes when compared with previous

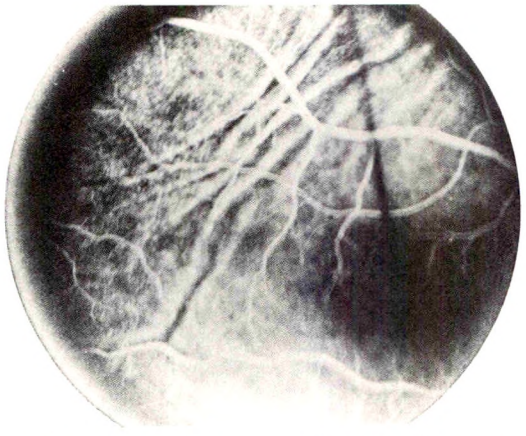


Fig. 5 (Cangemi, Trempe, and Walsh). Fluorescein angiography study of case shown in Figure 2, top left. Irregular folds are seen temporal to the macular region in the late venous phase.

studies. Hyperopia was the leading factor in our series. Also, in five cases in which there was a difference in hyperopic correction between the two eyes (from 1 to 4 prism diopters), an orbital or ocular tumor was found to be the cause. Because these studies were conducted at two large retinal centers, we were not surprised by the number of cases associated with scleral buckling procedures. There was a great variety of causes of choroidal folds, but in ten cases no definite cause could be established. This further emphasizes the need for careful long-term follow-up of these patients.

Numerous theories have arisen as to the possible etiology of choroidal folds (Table 3). Some of the factors proposed thus far are localized scleral shortening, scleral shrinkage, increased scleral thickness, increased choroidal thickness making the overlying Bruch's membrane redundant and forcing it and the retinal pigment epithelium into folds, compromise of choroidal vasculature, choroidal engorgement, and a combination of an anatomic attachment of Bruch's membrane to the underlying choriocapillaris and some factor that causes congestion in the choriocapillaris.[1,2,4,5,7,16,19]

Summary

We documented the presence of choroidal folds in a series of 59 eyes. Fifteen separate conditions were established as causes of the choroidal folds. Hyperopia was the most common cause, although no definite etiology could be established in ten cases.

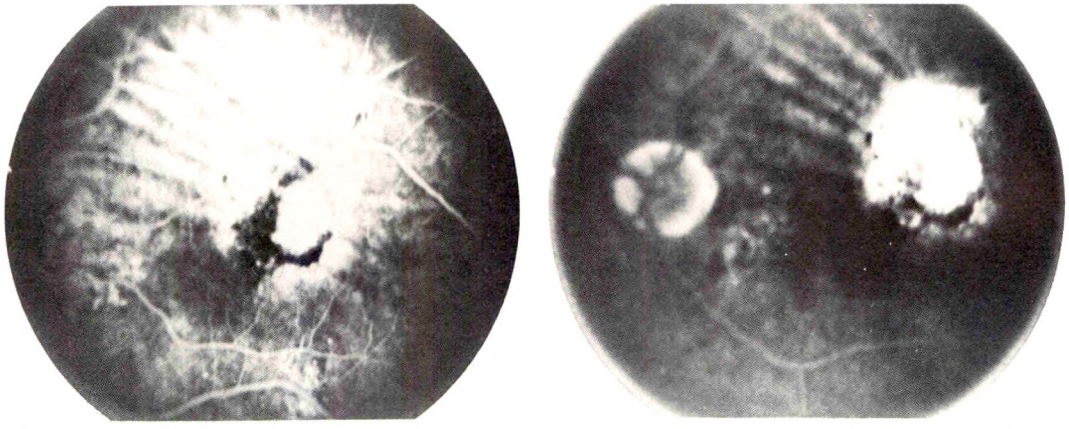


Fig. 6 (Cangemi, Trempe, and Walsh). Left, Fluorescein angiography study of same case as shown in Figure 2, top right. In venous phase, alternating hyperfluorescent and hypofluorescent streaks are seen. Intense staining and leakage is present in the macular region. Right, Late films again show no leakage in the areas of choroidal fold formation.

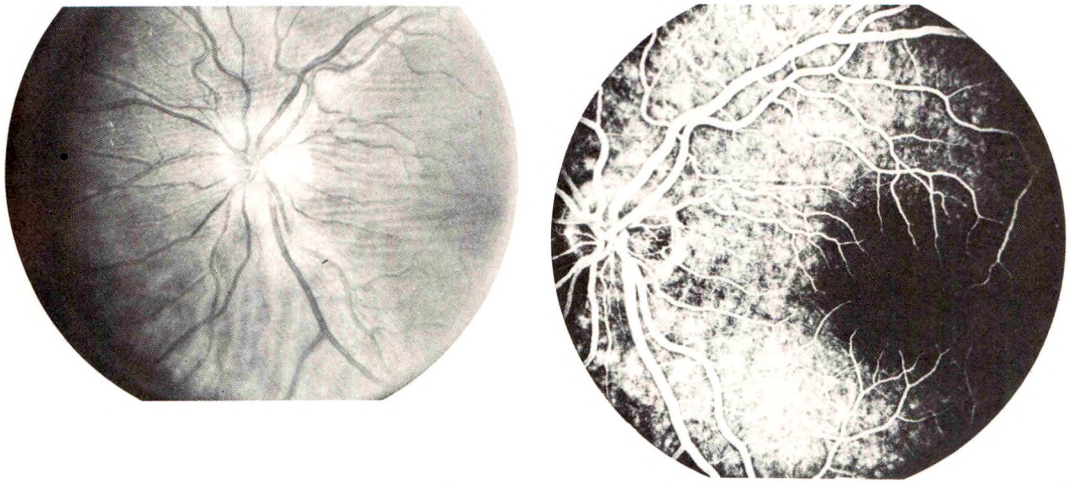


Fig. 7 (Cangemi, Trempe, and Walsh). Left, Retinal folds. Ophthalmoscopically, they resemble choroidal folds. Right, Venous phase of fluorescein angiography study. The absence of the alternating hyperfluorescent and hypofluorescent streaks clearly differentiates retinal folds from choroidal folds.

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ENDOGENOUS INTRAOCULAR *NOCARDIA ASTEROIDES* IN HODGKIN'S DISEASE

GARY S. LISSNER, M.D., RICHARD O'GRADY, M.D.,
AND
EARL CHOROMOKOS
Chicago, Illinois

Nocardia asteroides is a slow-growing aerobic organism with partially acid-fast, gram-positive branched filamentous hyphae and is classified as bacteria. *Nocardia* produces infections in man that range from chronic benign skin lesions and focal acute limited pulmonary inflammations to chronic progressive pulmonary infections with hematogenous spread to involve any tissue of the body, especially the central nervous system.[1-4]

Previously, eight cases of endogenous and one case of exogenous (postcataract extraction) intraocular *Nocardia* have been reported.[5-11] Some of these reports suggest that chronic debilitation or immunosuppression may predispose to endogenous intraocular *Nocardia* infection.[5-11] We studied a case of endogenous intraocular *N. asteroides* in a patient with a probable chronic neoplastic disease associated with altered host immunity.[12-15] To our knowledge, this is the first report describing the fluorescein angiographic findings of an active *Nocardia* lesion.

CASE REPORT

We first saw the patient, a 60-year-old man, in February 1977 and found a chorioretinal mass lesion in his right eye. He had a history of a "severe pneumonia" in 1946 with residual radiologic changes in the left lung field. In December of 1973 and 1974, he had "flu-like" syndromes with low-grade fevers, malaise, and weight loss, followed by progressive fatigue. Early in 1975, the patient developed right cervical and axillary lymphadenopathy. Skin tests for coccidioides and tuberculosis were negative, whereas the chest x-ray films revealed right and left apical pleural thickening with fibrotic changes in the left mid and upper lung fields. Biopsy specimens of enlarged cervical and axillary lymph nodes revealed regions of central necrosis surrounded by macrophages, lymphocytes, and foreign body giant cells. PAS and acid-fast stains were negative, as were aerobic and anaerobic cultures. Bronchoscopy was performed, but cultures of bronchial secretions were negative for acid-fast bacilli and fungi, and the carinal mucosa biopsy specimen was normal. The patient began receiving isoniazid and ethambutol for presumed tuberculosis.

In November 1975, the patient developed bilateral cervical lymphadenopathy. The purified protein derivative skin test and multiple sputum collections for acid-fast bacteria, bacterial and fungal cultures, and cytology were negative. A bone marrow biopsy revealed a hypocellular marrow with no granulomas. A lumbar puncture was normal. The patient was discharged and was given isoniazid and rifampin for presumed tuberculosis.

When he was readmitted to the hospital in September 1976, he had weakness, night sweats, and cervical, axillary, and inguinal lymphadenopathy. A second bone marrow aspirate showed only decreased iron stores, and a bone biopsy specimen was normal. A liver biopsy disclosed a healing granuloma with no acid-fast bacteria or fungi apparent on special stains. The lymphangiogram revealed abnormal iliac and periaortic nodes. Upper and lower gastrointestinal studies and proctoscopy were normal. A skin test anergy battery was positive only for *Trichophyton*. The patient was now thought to have sarcoidosis and was discharged with prescriptions for 60 mg/day of prednisone and isoniazid and rifampin.

The patient continued taking medication, but in February 1977, he was readmitted with an eight-day history of shaking chills, morning temperatures to 39.4° C, slightly blood-tinged sputum, and increasing dyspnea. His white blood cell count was 11,500 mm^3 and hemoglobin was 10.9/100 ml. On admission he had mild injection and discomfort in his right eye and received 10% sulfacetamide drops. When we saw him, the patient claimed his right eye had improved considerably.

Ophthalmologic examination revealed a best corrected visual acuity of 6/6 (20/20) in each eye. The orbits, exophthalmometry readings, and extraocular motions were normal. The bulbar conjunctiva of the right eye was slightly injected, but had no papillae or follicles. The corneas, scleras, anterior chambers, and irides were unremarkable. Intraocular pressure

From the Department of Ophthalmology, Northwestern University Medical School, Chicago, Illinois.

Reprint requests to Richard O'Grady, M.D., Department of Ophthalmology, Northwestern University Medical School, 303 E. Chicago Ave., Chicago, IL. 60611.

as measured by applanation tonometry was 16 mm Hg bilaterally. Ophthalmoscopic examination of the right fundus revealed a ten-disk diameter elevated off-white chorioretinal mass with an irregular surface and superficial hemorrhages four disk diameters nasal to the disk (Fig. 1). No vitreous reaction was noted over the mass. No other lesions were found in the right fundus, and examination of the left fundus revealed no abnormalities.

Ultrasound examination performed by the A-scan and contact B-scan modes delineated the mass in the right eye, but because it was only mildly elevated, no interpretations could be made. Fluorescein angiography showed in the early phases choroidal hypofluorescence in the involved area of the right fundus caused by blockage by a choroidal mass, and apparent retinal pigment epithelium elevation. Subsequent photographs showed a lack of fluorescence of retinal vessels over the mass. Later films showed leakage of fluorescein through the retinal pigment epithelium and through apparently altered retinal capillaries at the margins of the mass (Fig. 2). Late phase photographs showed leakage of dye into the vitreous (Fig. 3). The fluorescein angiogram was interpreted as showing a nonvascularized choroidal mass with involvement of the overlying retinal pigment epithelium, retina, and vitreous in the right eye.

The patient became increasingly dyspneic and chest x-ray films showed progressive pulmonary infiltration. Multiple sputum samples for acid-fast and fungal stains and cytology were negative. Fungal cultures were contaminated by bacteria. Sputum bacterial cultures grew alpha-streptococci, *Pseudomonas aeruginosa*, and *Enterobacter cloacae*. The patient developed progressive respiratory insufficiency and died Feb. 20, 1977.

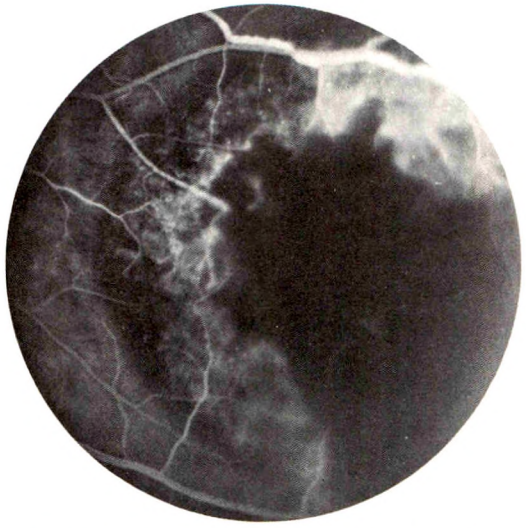


Fig. 2 (Lissner, O'Grady, and Choromokos). Midphase fluorescein angiogram demonstrating blockage of fluorescein over the mass with leakage at margins of mass.

Results

At postmortem examination, chronic, purulent necrotic lesions were found throughout both lung fields, in the thyroid, in the spleen, and in the kidneys. Microscopic examination of the lungs showed multiple focal nodules of acute

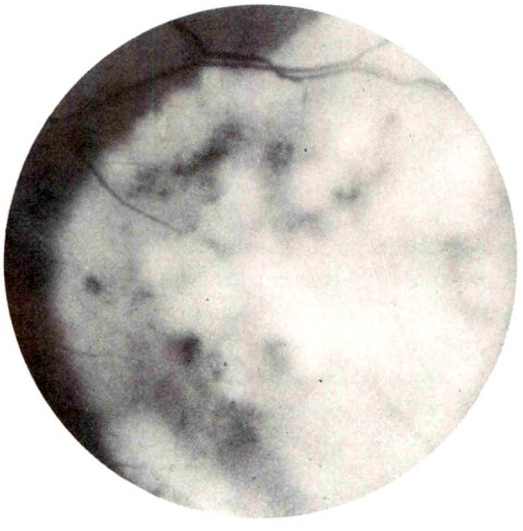


Fig. 1 (Lissner, O'Grady, and Choromokos). Off-white irregular mass nasal to disk of right eye.

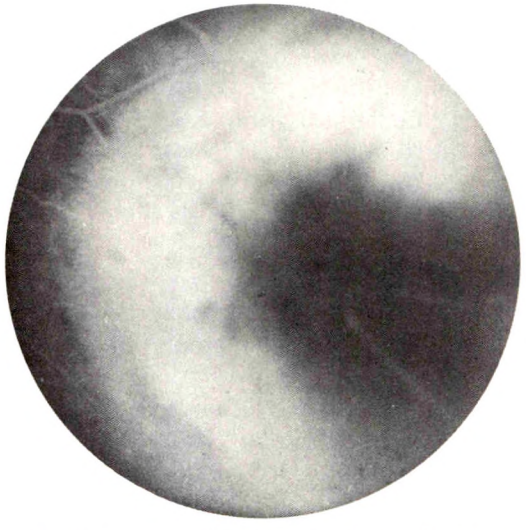


Fig. 3 (Lissner, O'Grady, and Choromokos). Late fluorescein angiogram with leakage into vitreous.

inflammation and abscess formation with acute pleuritis. Gomori methenamine silver stains of pulmonary tissue showed many branching filaments consistent with *Nocardia.* Cultures of the lung tissue grew *N. asteroides.* The thyroid and kidneys showed discrete areas of acute inflammation and abscess formation. Areas of focal hyalinization and fibrosis with depletion of lymphocytes were noted in the lymph nodes. The spleen showed areas of acute and chronic inflammation and necrosis, with abundant histiocytes and somewhat atypical histiocytic cells consistent with Hodgkin's disease. Gomori methenamine silver and Gram stains on tissue from the initial lymph node biopsies from 1975 were negative. The final pathologic diagnosis was Hodgkin's disease with disseminated nocardiosis caused by *N. asteroides* with involvement of the lungs, thyroid, spleen, and kidneys.

Gross examination of the right eye revealed a yellow-white chorioretinal mass, 12 mm in diameter, nasally between the optic disk and equator.

Microscopic examination of the right eye revealed a normal anterior segment. Nasal to the optic nerve a necrotic, suppurative inflammatory process replaced the choroid and extended into the subretinal pigment epithelial space through gaps in the pigment epithelium to involve most of the overlying retina (Fig. 4). Most of the cells in this area were polymorphonuclear leukocytes, but scattered lymphoctyes and plasma cells were present. Epithelioid and giant cells were not noted in any sections studied. The necrosis was especially intense in the area immediately adjacent to Bruch's membrane, where the choriocapillaris and innermost choroidal vessels appeared totally obliterated, and nuclear debris from disintegrating cells was prominent. Bruch's membrane appeared intact, but the area between

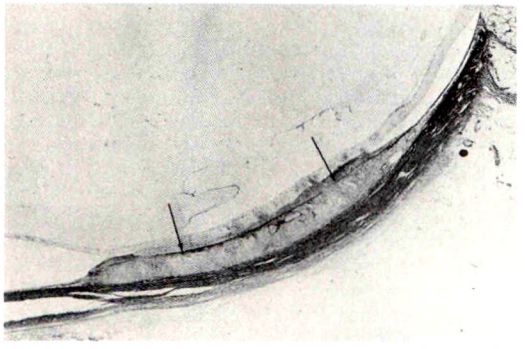


Fig. 4 (Lissner, O'Grady, and Choromokos). Necrotic choroid and retina surround a discontinous retinal pigment epithelial layer (arrows). The inner retina contains dilated vascular channels adjacent to the active inflammatory focus (hematoxylin and eosin, × 80).

Bruch's membrane and the disintegrating retinal pigment epithelium was filled with amorphous material. The overlying retina was necrotic, but the internal limiting membrane was intact. Away from the well defined inflammatory process, the other retinal and choroidal structures appeared free of involvement. The vitreous body adjacent to the chorioretinal process was infiltrated with mononuclear cells. The sclera external to the inflammatory process was essentially normal, although inflammatory cells extended down various emissary canals to involve episcleral tissues. The optic nerve was distorted by hydropic degeneration, but the lamina cribosa was level and the optic nerve substance was unremarkable. There was no evidence of any extension of the process elsewhere in the posterior portions of the globe or in the anterior segment.

Gomori methenamine silver stains revealed clusters and clumps of slender branching rodlike or filamentous structures along the inner surface of Bruch's membrane in the choriocapillaris and scattered in the adjacent choroid (Fig. 5). These filamentous structures were primarily confined to the choroid and subretinal pigment epithelial space, but a



Fig. 5 (Lissner, O'Grady, and Choromokos). Slender branched twisted filamentous structures extend into the subretinal space from a partially obliterated choriocapillaris. The choriocapillaris is patent at arrow C (Gomori methenamine silver, × 640).

few were found within overlying necrotic retina. The filaments were found to be gram-positive and mildly acid-fast. No filaments extended into the vitreous. The filamentous structures appeared consistent with *Nocardia.*

Gross and microscopic studies of the left eye were essentially normal.

Discussion

The generalized disease form of nocardiosis in the United States and Western Europe is usually caused by *N. asteroides.*[2,3] *Nocardia* is found worldwide in the soil and is thought to cause initial infection by inhalation, ingestion, or traumatic introduction.[2,16] On culture, the colonial forms are aerobic and resemble saprophytic mycobacteria.[3] Microscopically, the *Nocardia* organisms usually resemble filamentous hyphae with branches at 90-degree angles, but the filaments may fragment into bacillary and coccoidal forms.[2–4, 17]

Nocardia infections cause inflammatory responses that resemble those caused by pyogenic bacteria, with gray-white confluent abscesses. Generally, many polymorphonuclear leukocytes fill the abscesses. Some fibrin, lymphocytes, plasma cells, and, occasionally, central necrosis also may be present. There is little or no evidence of giant cells, fibrosis, or caseation. The gram-positive *Nocardia* filaments are found within the abscess cavities.[2,3,17] McCarthy, Kennedy, and Hazard[18] implanted *N. asteroides* in the subconjunctival spaces and in the anterior chambers of rabbits. In seven of 12 eyes (58%), they produced tan nodules that microscopically showed purulent granulomas with areas of microabscesses.

Nocardiosis is no longer considered an obscure disease and appears to be increasing in incidence.[3,4] In 1955, McQuown[19] estimated that in 5% of the patients in tuberculosis hospitals, diagnosis of nocardiosis had been missed. An erroneous diagnosis of tuberculosis can be made because *Nocardia* may be difficult to isolate and culture, and because *N. asteroides* hyphae may fragment into short bacillary forms that show variable acid-fastness on staining.[2–4,19] Special isolation and acid-fast staining techniques must be used to demonstrate the presence of *Nocardia.*[4] The organisms do not stain with hematoxylin and eosin or PAS, but are revealed by Gram and Gomori methenamine silver stains.[2] In 1976, after conducting a survey, Beaman[1] concluded that *Nocardia* infections were not rare, and estimated an incidence of 500 to 1,000 clinically significant cases each year. The increasing incidence of *Nocardia* infections is probably a result of better detection and increased numbers of susceptible immunosuppressed patients.[1,3]

In our case, the autopsy diagnosis was Hodgkin's disease with disseminated no-

cardiosis involving the lungs, thyroid, spleen, kidneys, and right eye. It was uncertain how long the patient harbored *Nocardia*, but the infection was possibly promoted by the Hodgkin's disease and the corticosteroid therapy. Nocardiosis has been described as a primary disease and also as an opportunistic infection in patients with compromised immunologic responses.[1,20-22] Young and associates[22] found that of their patients with opportunistic *N. asteroides* infections, the largest group had advanced Hodgkin's disease. Because only one of these patients had marked granulocytopenia, they suggested that mononuclear immunity or delayed hypersensitivity was a significant component in the defense against *Nocardia*.[22] Many reports have been published concerning the abnormal immunocompetence of patients with Hodgkin's disease and their increased susceptibility to infections.[23-27]

Many chronically ill patients with *Nocardia* infections have also had corticosteroid therapy.[20,22] Cross and Chapman[20] found that nine of 44 cases (20.4%) with primary *Nocardia* infections or nocardiosis associated with a debilitating illness had received prolonged corticosteroid therapy. Corticosteroids are thought to affect the body's defenses against ocular infections.[28] Newmark, Polack, and Ellison[29] inoculated rabbit corneas with diluted suspensions of *N. asteroides* and found that eyes treated with dexamethasone drops had much more severe corneal infections. Mishra and associates[30] found that white mice given intravenous *Nocardia* had a higher and more rapid mortality with more extensive lesions when treated with intramuscular cortisone. The mean lethal dose for *N. asteroides* was seven times lower in the cortisone-treated mice.[30] Seven of the eight previously described cases of endogenous intraocular *Nocardia* had some related debilitating disease or injury.[5-11] Four of these patients were receiving some immunosuppressive therapy including corticosteroids before the *Nocardia* infection,[8-11] and two of them had diseases related to immunodeficiency.[10,11]

In our patient, ophthalmoscopic examination revealed an off-white chorioretinal mass in his right eye. No overlying vitritis was detected clinically. The lesion could not definitely be called inflammatory. Ultrasound A- and B-scans provided little diagnostic help in our patient. Fluorescein angiographic studies showed the presence of a nonvascularized choroidal mass with involvement of the overlying retinal pigment epithelium, retina, and possibly, vitreous. Fluorescein had leaked through the retinal pigment epithelium and retinal capillaries surrounding the mass. Burpee and Starke[7] found no fluorescein leakage from inactive peripheral lesions after treatment and recovery of a patient reported to have had bilateral metastatic intraocular *N. asteroides*. In contrast, the fluorescein leakage noted in our patient suggests an active lesion. The ocular pathology studies in our patient revealed an active nongranulomatous, suppurative endogenous chorioretinitis associated with a mild overlying vitritis.

On the Gomori methenamine silver stain of the right eye, filaments consistent with *Nocardia* organisms were clustered along Bruch's membrane and within the choriocapillaris. This would seem to indicate that they arrived via the choroidal, rather than the retinal circulation. *Nocardia* shows vascular involvement and hematogenous metastatic abscess formation from the lung to the central nervous system.[1] With an overwhelming systemic fungus infection and hematogenous spread, one might expect eye involvement.[31] Similarly, such involvement appears to occur with nocardiosis.

As illustrated by our patient, the diagnosis of nocardiosis is often difficult. The diagnosis is usually not considered until the organism has been recovered, which may require special techniques.[3,4] A patient suspected of having a *Nocardia* infection might harbor an intraocular *Nocardia* chorioretinitis.[5–11] If the patient's immunologic defenses were compromised by disease or medication, the suspicion of nocardiosis might be enhanced.[20–22,29,30] Clinical and fluorescein angiographic findings similar to those presented in this report could suggest or further strengthen a suspicion of nocardiosis. Such a suspicion may allow more aggressive diagnostic procedures and treatment.

SUMMARY

A 60-year-old man receiving antituberculous and corticosteroid therapy for a granulomatous disease of uncertain etiology was found to have a chorioretinal mass in his right eye. Fluorescein angiography showed blockage of fluorescence by the mass and late leakage. Autopsy findings were compatible with Hodgkin's disease with disseminated nocardiosis caused by *Nocardia asteroides*. Organisms typical of *Nocardia* were found in the choroid and subretinal space. The patient's history, ophthalmic examination, and fluorescein angiographic findings suggested a type of chorioretinal involvement.

ACKNOWLEDGEMENT

Barton Hodes, M.D. provided the ultrasonographic studies.

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OPHTHALMIC MINIATURE

"What's the blood type,"

"Type one, sergeant."

"Does it check,"

"No, Reeves is type three."

"Oho! Phone the main lab. We'll take him into town for a retinal."

I was caught cold and knew it. They knew positively that I wasn't Reeves. Once they photographed the pattern of blood-vessels in the retina of either eye they would know just as certainly who I really was, in no longer time than it took to radio the picture to the Bureau of Morals and Investigation—less, if copies had been sent out to Denver and elsewhere with the tab on me.

Robert A. Heinlein, *Revolt in 2100*
Street & Smith, 1939

IMMUNE COMPLEXES IN RETINOBLASTOMA

DEVRON H. CHAR, M.D., AND MARY CHRISTENSEN, B.A.
San Francisco, California
LEON GOLDBERG, M.D.
Johannesburg, South Africa
AND
PAUL STEIN, PH.D.
San Francisco, California

Immune complexes have been demonstrated in both animal and human malignancies.[1-3] In the animal models antigen-antibody immune complexes can be demonstrated to block cell-mediated cytotoxicity.[4] With the advent of more sensitive immune complex assays, a number of human malignancies have been studied, and immune complexes have been detected in the sera of many cancer patients.[5,6] The level of immune complexes has corresponded to tumor burden and prognosis in some patients with solid tumors, lymphomas, and leukemias.[7,8]

Some clinical observations support the hypothesis that immune factors play a role in the pathophysiology of retinoblastoma. Spontaneous regressions of both intraocular and extraocular retinoblastoma have been reported in over 50 patients; nonischemic tumor necrosis has been observed histologically in some of these tumors.[9,10] Additionally, some patients have retinoblastoma cells in their systemic circulation at the time of enucleation and do not develop metastases.[11]

From the Ocular Oncology Unit, Department of Ophthalmology and the Francis I. Proctor Foundation, University of California, San Francisco (Drs. Char and Stein, and Ms. Christensen); and the Department of Ophthalmology, University of Witwatersrand Medical School, Johannesburg, South Africa (Dr. Goldberg). This study was supported in part by National Institutes of Health Grants EY01759, EY02072, and EY01441 (Dr. Char). Dr. Char is a Research and Career Development Awardee (1 K04 EY00117).

Reprint requests to Devron H. Char, M.D., Ocular Oncology Unit S315, University of California, San Francisco, San Francisco, CA 94143.

We studied a group of retinoblastoma patients with a modification of the Raji cell radioimmunoassay to determine whether immune complexes are present in the serum of these patients and if the level of these immune complexes corresponds to the disease status and prognosis.

MATERIAL AND METHODS

Serum was obtained from a group of retinoblastoma patients and controls examined at the Ocular Oncology Unit of the University of California, San Francisco, and at the Department of Ophthalmology, University of Witwatersrand, Johannesburg, South Africa. All patients had a standard ocular oncology examination and a systemic examination for metastatic disease. In most patients we used computed axial tomography, cerebral spinal fluid and bone marrow examinations, bone scans, and serum chemistries. Patients 7, 11, and 12 had histologically documented metastatic retinoblastoma (Table 1). Patients 5, 6, and 8 had unilateral retinoblastoma without metastatic disease. All other patients had bilateral retinoblastoma.[12]

After informed consent was obtained from the parents of each patient, blood was drawn for routine hematologic studies and immune complex determinations. These immune complex studies were also performed on normal controls and, where possible, age-matched controls with nonmalignant ocular lesions.

The immune complex levels in the

TABLE 1

CLINICAL STATUS AT IMMUNE COMPLEX DETERMINATION

Patient No.	Ocular Involvement	Metastatic Disease
1	Bilateral inactive disease after therapy	Negative
2	Bilateral disease, after unilateral enucleation with active disease in fellow eye	Negative
3	Bilateral disease status post-radiation	Negative
4	Bilateral disease status post-enucleation one eye, active disease fellow eye	Negative
5	Unilateral tumor pre-enucleation	Negative
6	Unilateral tumor pre-enucleation	Negative
7	Bilateral disease with intracranial involvement	Positive
8	Unilateral tumor pre-enucleation	Negative
9	Bilateral disease pre-therapy	Negative
10	Bilateral disease status post-enucleation, one eye, active disease in fellow eye.	Negative
11	Metastatic retinoblastoma	
12	Metastatic retinoblastoma with orbital involvement	
13	Unilateral disease after enucleation	

serum were determined by using a modification of the Raji radioimmunoassay described in detail by Theofilopoulos, Willson, and Dixon[13] (Figure). Twenty-five microliters of patients' sera was diluted 1:4 with normal saline and incubated with 2×10^6 Raji cells that were at the 72-hour stage of propagation. After 45 minutes of incubation at 37° C, the Raji cells were washed three times with minimal essential media and a standardized amount of radioactive-labeled iodine (^{125}I) rabbit antihuman immunoglobulin and 1% human serum albumin was added. An additional period of incubation with gentle agitation was carried out at 4° C × 30 minutes; then the Raji cells were washed repeatedly, and the radioactivity of the cell pellet determined. The concentration of immune complexes in the test sera was extrapolated from a standard curve to which various known amounts of aggregated human gammaglobulin and complement were incubated with Raji

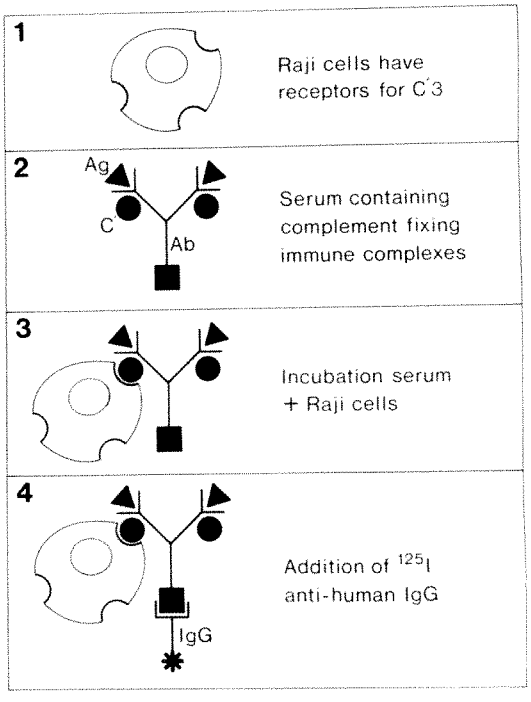


Figure (Char and associates). Schematic diagram of Raji cell radioimmunoassay for immune complexes.

cells and radioactive-labeled antihuman immunoglobulin. The amount of immune complexes was expressed as microgram equivalents of aggregated human gammaglobulin per milliliter of serum. The replicates varied by less than 5% in almost all cases, and normal controls performed sequentially had excellent reproducibility. Statistical analysis was performed by using the Mann-Whitney test.[14]

Results

Five patients with retinoblastoma had normal levels of immune complexes in their sera (Table 2). Three of these patients had unilateral retinoblastomas with no evidence of metastasis, and two patients had metastases. Eight of 13 patients with retinoblastoma had increased levels of immune complexes. One of three patients with metastatic retinoblastoma had increased levels of immune complexes. The patient with the highest level of immune complexes had no clinically detectable metastatic disease.

TABLE 2

IMMUNE COMPLEX CONCENTRATIONS IN RETINOBLASTOMA

Patient No.	Immune Complex Concentrations (μg AHG/ml)*
1	160
2	>3500
3	17
4	135
5	77
6	36
7	60
8	58
9	215
10	72
11	11
12	20
13	12
Mean of control group	10.6±7.6†

*Aggregated human gammaglobulin equivalen per milliliter.

†Statistically significant difference between retinoblastoma and controls ($P < .01$).

In previous work using this assay in our laboratory, the immune complex levels of 90% of normals were less than 20 μg of aggregated human gammaglobulin per milliliter. The levels of immune complexes in the retinoblastoma patients' sera was significantly greater than the levels in control subjects' sera ($P < .001$). Specifically, three age-matched controls (one each with persistent hyperplastic primary vitreous, uveitis, and congenital cataract) had immune complex levels less than 20 μg of aggregated human gammaglobulin per milliliter.

A partial characterization was performed on immune complexes from Patient 5 by using 3% polyethylene glycol and immunoelectrophoresis; this patient's immune complexes consisted of both IgG and IgM antibodies.

Discussion

We have demonstrated that patients with retinoblastoma have statistically significant increased levels of immune complexes in their serum. The chemical nature, antigenic composition, and biologic importance of these complexes remain to be determined. Investigators have demonstrated immune complexes in 12 to 93% of patients with many human tumors including leukemias, lymphomas, melanoma, sarcoma, nasopharyngeal carcinoma, prostate cancer, and colonic carcinoma.[1-3,5-8,15,16] In this study 62% of retinoblastoma patients had increased levels of immune complexes.

In some human malignancies the level of immune complexes corresponds to both tumor burden and prognosis. Theofilopoulos and associates[17] studied a group of systemic melanoma patients with various amounts of residual tumor. Using the Raji cell assay, they noted that the immune complex level corresponded to the disease status and tumor burden. Similarly, the level of immune complexes determined at diagnosis and after therapy

corresponded to the prognosis in both leukemia and breast cancer patients.[7,8] Although the correlation between the level of immune complexes and these prognostic variables is significant, some discrepancies have been observed. We were unable to demonstrate a statistically significant correlation between the level of immune complex and disease status in retinoblastoma patients studied, but data from other investigators suggest a much larger group would have to be surveyed to determine if this correlation exists. Furthermore, because many of our patients have only been tested once and were not subject to long-term follow-up, we may have missed any correlation between immune complexes and disease status if it exists.

Baldwin, Price, and Robin[18] demonstrated in a rat hepatoma model that circulating immune complexes consisting of tumor-associated antigens and antibodies blocked cell-mediated immunity in vitro. In some patients with progressive tumors, Hellström and Hellström[4] and others[5–19] demonstrated that blocking factors of a similar composition abrogate cell-mediated immunologic responses to tumor antigens. Using a modification of the Raji cell assay, Theofilopoulos and associates[17] showed that patients with melanoma, sarcoma, and colonic carcinoma have immune complexes that consist of tumor-associated antigens and IgG.[17] In that study, the size of immune complexes appears to be between 11 and 19 S; however, using other techniques, some investigators have demonstrated larger complexes.[6] In retinoblastoma patients, we have demonstrated the presence of immune complexes; in most patients the complexes consist of either IgG alone or IgG and IgM antibody molecules combined with antigens. These antigens are, most likely, retinoblastoma-associated; however, until we can characterize them further, this is unproven.

Other extraneous factors probably were not responsible for the increased levels of immune complexes measured by this assay. Because aggregated immunoglobulin can yield positive Raji cell radioimmunoassay results, all sera tested in this study were frozen and thawed once to attempt to decrease the possibility of immunoglobulin aggregation. We have deliberately and repeatedly frozen and thawed a number of sera containing both normal and increased levels of immune complexes and have not noted a marked change in immune complex levels. Similarly, whereas antilymphocyte antibodies could give a false-positive reaction in the Raji cell assay, most of these antibodies are the cold type; because the Raji cell test is run at 37° C, these antibodies probably are not responsible for the activity observed.[20,21]

Detection of increased levels of immune complexes in patients with retinoblastoma has potential clinical implications. First, in patients with leukocoria, this assay, which requires less than 0.1 ml of serum, may prove useful as a diagnostic adjuvant. Similarly, the levels of immune complexes may correspond to the prognosis and metastatic disease status. Finally, the use of tumor-associated antigens separated from these immune complexes may lead to even more sensitive assays of tumor-related immunity, useful for the immunologic diagnosis and monitoring in patients with retinoblastoma.

Summary

Thirteen patients with retinoblastoma were tested for circulating immune complexes using the Raji cell radioimmunoassay. Eight of 13 patients had statistically significantly increased levels of immune complexes.

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AN UNUSUAL CASE OF METASTATIC CARCINOMA TO THE EYELID

JOHN GRAHAM, M.D., SUE ELLEN YOUNG, M.D., AND MARIO LUNA, M.D.
Houston, Texas

Metastasis of the eyelids is rare. The incidence is approximately 1.4% of all malignant eyelid neoplasms.[1] Until Riley [2] reviewed the material in the Mayo Clinic tissue registry from 1922 to 1969, only 15 cases had been reported as having occurred in an unusual population of patients with primary tumors including those of the trachea and the parotid gland. These cases created a distorted picture of which tumors were likely to metastasize to the eyelid. However, the 15 cases added by Riley helped change the perspective by showing that the incidence of tumors metastasizing to the eyelid more closely reflected the previously recognized incidence of those that metastasize to the skin. Ten of the first 30 cases were from carcinoma of the breast, six were from malignant melanoma of the skin, and five were from the lung.

Riley defined three characteristic forms of metastatic lesions of the eyelid: (1) a solitary subcutaneous nodule, nontender and uninflamed (the most common form of metastatic malignant melanoma, which occurred in only one case of metastatic breast carcinoma); (2) a nontender, diffuse thickening and induration of the eyelid (the most common form in metastasis from breast carcinoma); (3) an ulcerative lesion (manifested by metastatic squamous cell carcinoma of the lung and by metastatic adenocarcinoma of the stomach).

In 1973 Hood, Font, and Zimmerman[3] reviewed 13 cases of carcinoma of the breast metastatic to the eyelid. Over half of the cases presented diagnostic problems for which they gave three reasons: (1) the lesion in the eyelid was detected before the primary tumor; (2) it was the first sign of metastasis after an apparently curative mastectomy; and (3) it demonstrated a histiocytoid histologic pattern that resembled a benign histiocytic lesion.

Of these 13 patients, eight came to the office after diffuse inflamed, painless swelling, and five had painless subcutaneous mobile nodules. The diagnosis of metastatic carcinoma was not made in nine of the 13 cases by the primary physician and pathologist.

Metastatic disease to the eyelid has been reported as mimicking a chalazion[4] and as an uncommon cause of eyelid swelling.[5] Most breast metastases to the eyelid occur as diffuse swelling. Of the described cases that had nodules, all have been classified as subcutaneous. No reported case has had a clinical appearance that could be confused with basal cell carcinoma, sebaceous gland carcinoma, or similar primary eyelid malignancy. Our case is unusual in that it was clinically confused with a primary eyelid malignant neoplasm.

CASE REPORT

In June 1972, a 46-year-old woman found a 2-cm mass in the right breast at about the 12 o'clock position. Her family history was noncontributory for breast cancer.

She had a right radical mastectomy one week later, and axillary lymph nodes were positive for breast carcinoma. Postoperative radiation therapy was given, and she was observed until October 1975, when she began having severe pelvic and back pain. X-ray films showed multiple osteoblastic metastases in the bony pelvis and collapse of the tenth thoracic vertebral body. Bone scan was positive in these areas. In December 1975, she underwent bilateral salpingoophorectomy, and in February 1976, she received 3,000 rads of radiation therapy to the lower thoracic spine.

From the Department of Surgery (Ophthalmology) (Drs. Graham and Young), and the Department of Pathology (Dr. Luna), M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

Reprint requests to Sue Ellen Young, M. D., M. D. Anderson Hospital and Tumor Institute, 6723 Bertner Dr., Houston, TX 77030.

She had some temporary regression of pain, but by September 1977, the bone disease and pain had progressed. She was then referred here for further examination and treatment. In the course of her examination, she was referred to the Ophthalmology Clinic because of a right lower eyelid lesion.

A nodule had been present on her right lower eyelid for about one year. Her primary ophthalmologist had told her it was a "blocked duct." The lesion had started as a small "stye-like" eruption. It was painless and occasionally would swell slightly and have a small amount of drainage. It gradually increased in size over the year.

On examination, there was a firm, discrete, nodular lesion on the medial portion of the right lower eyelid, measuring 10 × 7 mm. It involved the full thickness of the eyelid including the margin and inferior punctum (Fig. 1). No ulceration or signs of inflammation were present, and cilia were absent over the lesion.

The remainder of her ophthalmic examination was normal. There were no signs of choroidal or orbital metastases. The clinical diagnosis of her eyelid lesion was probable basal cell carcinoma or sebaceous gland carcinoma with metastatic disease.

Incisional biopsy was performed through a skin approach and submitted for analysis. A few days later, the patient died suddenly. Autopsy confined to the brain revealed the immediate cause of death to be massive subarachnoid and intraventricular hemorrhage secondary to a ruptured berry aneurysm.

The eyelid biopsy revealed breast carcinoma metastatic to dermis (Fig. 2). Additional tissue obtained post mortem from a conjunctival approach confirmed the full thickness extent of the lesion (Fig. 3).

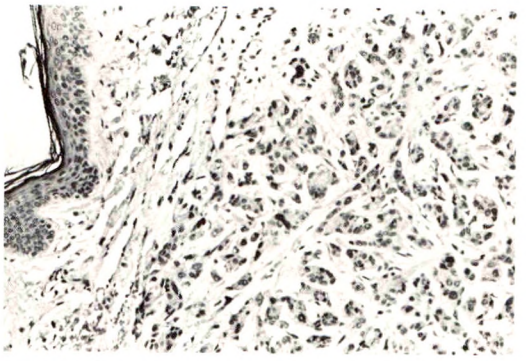


Fig. 2 (Graham, Young, and Luna). Skin of eyelid demonstrating metastatic breast carcinoma in dermis. Cells arranged in ductal structures and solid nests (hematoxylin and eosin, × 150).

Discussion

Carcinoma of the breast is the most common malignant neoplasm in women and outnumbers all other malignant neoplasms in both sexes. Of newborn girls, 6.9% or one in 14 will develop breast cancer in their lifetime. The annual death rate from breast cancer is over 20 per 100,000 women.[6] The magnitude of the problem was demonstrated by Bloch and Gartner[7] who found one third of patients with systemic breast carcinoma to have metastases to the eye or orbit. Therefore, any time an unusual lesion is found in a woman, metastasis from carcinoma of the breast should often be included in the differential diagnosis.

Lever[8] described four types of cutaneous metastases from breast cancer. These include inflammatory, telangiectatic, nod-

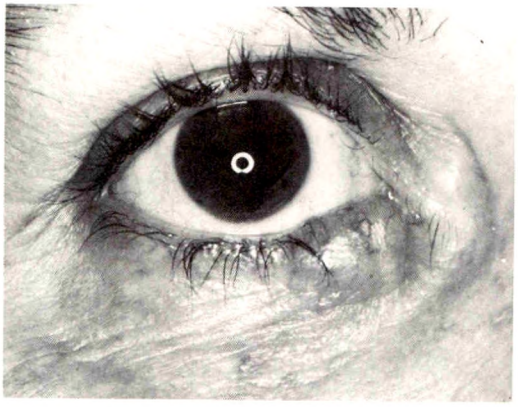


Fig. 1 (Graham, Young, and Luna). Nodular lesion at medial aspect of right lower eyelid, involving margin and inferior punctum.

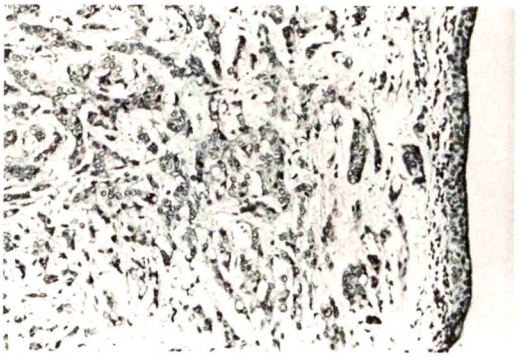


Fig. 3 (Graham, Young, and Luna). Conjunctival side of eyelid depicting metastatic mammary carcinoma. Note cells with vacuolated cytoplasm arranged in columns (hematoxylin and eosin, × 150).

ular, and en cuirasse. In the inflammatory form, the skin stimulates erysipelas with erythema and diffuse edema. The skin shows purple papules and pseudovesicles in the telangiectatic form. These two types of metastasis are usually seen if the progression of disease is occurring rapidly. The nodular form usually takes place when the disease is spreading slowly. Carcinoma en cuirasse refers to chest wall involvement by carcinoma of the breast.

Because primary skin tumors occur along the lines of adnexal structures, they may thus be differentiated from metastatic tumors, which are frequently subcutaneous with normal overlying epithelium.

Our case is unusual because the patient's eyelid lesion proved to be metastatic carcinoma and the metastatic lesion involved full thickness of the eyelid and was fixed to the overlying epithelium. The appearance of the lesion as a nonmobile, painless nodule at the eyelid margin and the course of its development created clinical confusion with a primary eyelid malignancy.

SUMMARY

A 46-year-old woman developed a painless nodular lesion of her right lower eyelid four years after having a right radical mastectomy for breast carcinoma. The lesion slowly increased in size over one year to involve full thickness eyelid tissue that included the margin and inferior punctum and was associated with localized loss of cilia. The clinical appearance of the lesion and its course of development suggested a primary eyelid neoplasm. Incisional biopsy revealed metastatic mammary carcinoma.

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CONJUNCTIVA IN ASYMPTOMATIC CONTACT LENS WEARERS

JACK V. GREINER, PH.D.
Boston, Massachusetts
HENRY I. COVINGTON, M.S.
Washington, D.C.
DONALD R. KORB, O.D., AND MATHEA R. ALLANSMITH, M.D.
Boston, Massachusetts

Wearing contact lenses may induce alterations of the upper palpebral tarsal conjunctival epithelium that are unrecognizable with biomicroscopy and ocular staining. This possibility is important in view of the report that giant papillary conjunctivitis associated with the wearing of hard or soft contact lenses of all types results in dramatic changes in the surface of the upper tarsal conjunctival epithelium.[1] We question whether or not the epithelial surface changes associated with giant papillary conjunctivitis result from mechanical rubbing of the contact lens on the upper tarsal conjunctiva or whether these changes are secondary to the disease process, or a combination of both factors. In an attempt to answer this question, we studied long-term, asymptomatic contact lens wearers. The criteria for subject selection included the following: subjects had no anterior ocular abnormalities and had upper tarsal conjunctivae of normal appearance and thickness without hyperemia, excessive follicular formation, or giant papillae formation even when examined with the highest biomicroscopic magnification.

The purpose of our investigation was (1) to study the epithelial surface of the upper tarsal conjunctiva in asymptomatic hard and soft contact lens wearers, and (2) to compare this epithelial surface to that of normal subjects[2] who had never worn contact lenses and to the epithelial changes in persons with contact lens-associated giant papillary conjunctivitis.[3]

SUBJECTS AND METHODS

We studied specimens of the upper palpebral tarsal conjunctiva from 11 asymptomatic contact lens wearers who had what appeared to be normal and particularly quiescent conjunctival surfaces (Fig. 1 and Table). Five wore hard contact lenses and six wore soft lenses made by various manufacturers. Two groups of previously described subjects were used for comparison: the first comprised 11 subjects[2] with no symptoms and normal conjunctivae, who had never worn contact lenses; the second consisted of 11 subjects[3] with contact lens-associated giant papillary conjunctivitis.

After local anesthesia (Table), biopsy specimens (approximately 2 x 2 mm) were shaved off the midcentral upper tarsal conjunctiva with a razor blade knife by cutting tangentially to the tarsal plate. No forceps were used, and the surface of the specimen was not touched. Biopsy specimens were slid onto the blade edge during cutting and from the blade edge onto

From the Department of Ophthalmology, Harvard Medical School, and the Department of Cornea Research, Eye Research Institute of Retina Foundation (Drs. Greiner and Allansmith), Boston, Massachusetts; the Ernest E. Just Laboratory of Cellular Biology, Department of Anatomy, Howard University College of Medicine (Mr. Covington), Washington, D.C.; and the New England College of Optometry (Dr. Korb), Boston, Massachusetts. This study was supported by Institutional National Research Service Award EY-07018 (Dr. Greiner), and grants EY-00208 and EY-01552 from the National Eye Institute, National Institutes of Health (Dr. Allansmith); the Massachusetts Lions Eye Research Fund, Inc. (Drs. Greiner and Allansmith); and a research grant from Bausch and Lomb (Dr. Allansmith).

Reprint requests to Jack V. Greiner, Ph.D., 20 Staniford St., Boston, MA 02114.

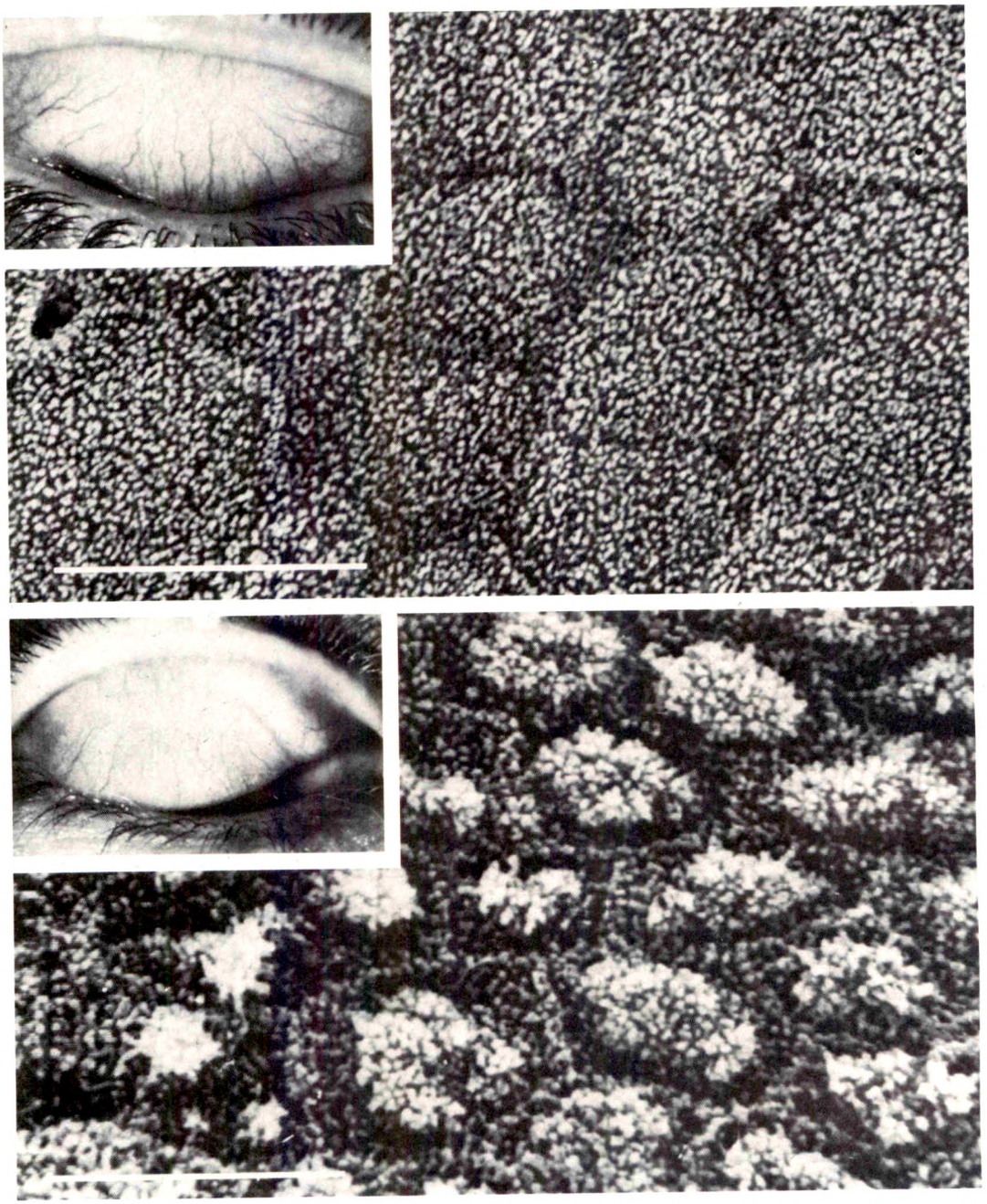


Fig. 1 (Greiner and associates). Top, Normal conjunctiva in non-lens wearer (bar gauge=10 μ; ×4,300). Inset, Clinical photograph of normal upper tarsal conjunctiva in non-lens wearer. Bottom, Conjunctival surface in asymptomatic lens wearer (bar gauge=10 μ; ×4,030). Inset, Clinical photograph of normal-appearing, asymptomatic lens wearer.

TABLE

SUBJECTS FOR BIOPSY OF UPPER TARSAL CONJUNCTIVA

Subject No.	Age (yrs)	Anesthesia Administered*	Contact Lens Type†	Years Worn‡
		Asymptomatic Contact Lens Wearers		
1	27	Nerve block	SCL	5
2	30	Nerve block	HCL	6
3	62	Nerve block	HCL	15
4	28	Nerve block	HCL	12
5	32	Nerve block	HCL	14
6	23	Nerve block	SCL	1
7	29	Nerve block and proparacaine	SCL	2.5
8	39	Proparacaine	SCL	3
9	30	Proparacaine	SCL	3
10	29	Nerve block	SCL	5.5
11	42	Proparacaine	HCL	8.5

*Van Lint nerve block with 2% xylocaine.
†SCL indicates soft contact lens; HCL, hard contact lens.
‡Years worn equals total contact lens experience including previous hard contact lens wearing experience.

a supporting piece of cardboard and mounted flat. Mounting the specimen on the cardboard prevented the tissue from folding.

Biopsy specimens were immediately immersed in 3% glutaraldehyde solution in 0.15M sodium cacodylate buffer, pH 7.2, at room temperature for three to four hours. The specimens were rinsed in buffer three times and refrigerated overnight. They were then dehydrated in graded ethyl alcohols, treated with a transitional fluid (Freon 113), and dried in a critical point drying apparatus using Freon 13 as a critical point transitional fluid. Specimens were mounted with silver conducting paint on aluminum stubs and coated with thin layers of carbon and gold-palladium in a sputter coater. Tissue was examined with a scanning electron microscope operated at 20 kV.

RESULTS

Although the clinical biomicroscopic appearance of the upper palpebral tarsal conjunctiva in asymptomatic contact lens wearers was identical to that of normal subjects (Fig. 1), examination by scanning electron microscopy revealed distinct anatomical differences. Regions of anatomically altered epithelial cell surfaces were interspersed among regions of normal cells in the asymptomatic lens wearers (Fig. 2). The altered cell surfaces had reduced cell diameters (4 to 6 μ) and showed centrally clumped microvilli (Fig. 3). Microvillar patterns ranged from anatomically normal microvilli (Figs. 3 and 4) to severely centralized microvilli (Figs. 5-8). Centralization of microvilli resulted in leaving the plasma membrane devoid of microvilli around the cell periphery and adjacent to the microvillar borders. Several tufted structures that consisted of small groups of microvilli were present in some cells (Fig. 4). Microvillar strands often extended from the cell borders to centralized microvilli (Figs. 6 and 7). Mucus was present both in ropelike strands and in particulate forms (Fig. 6). Mucus strands were often associated with the centralized microvilli

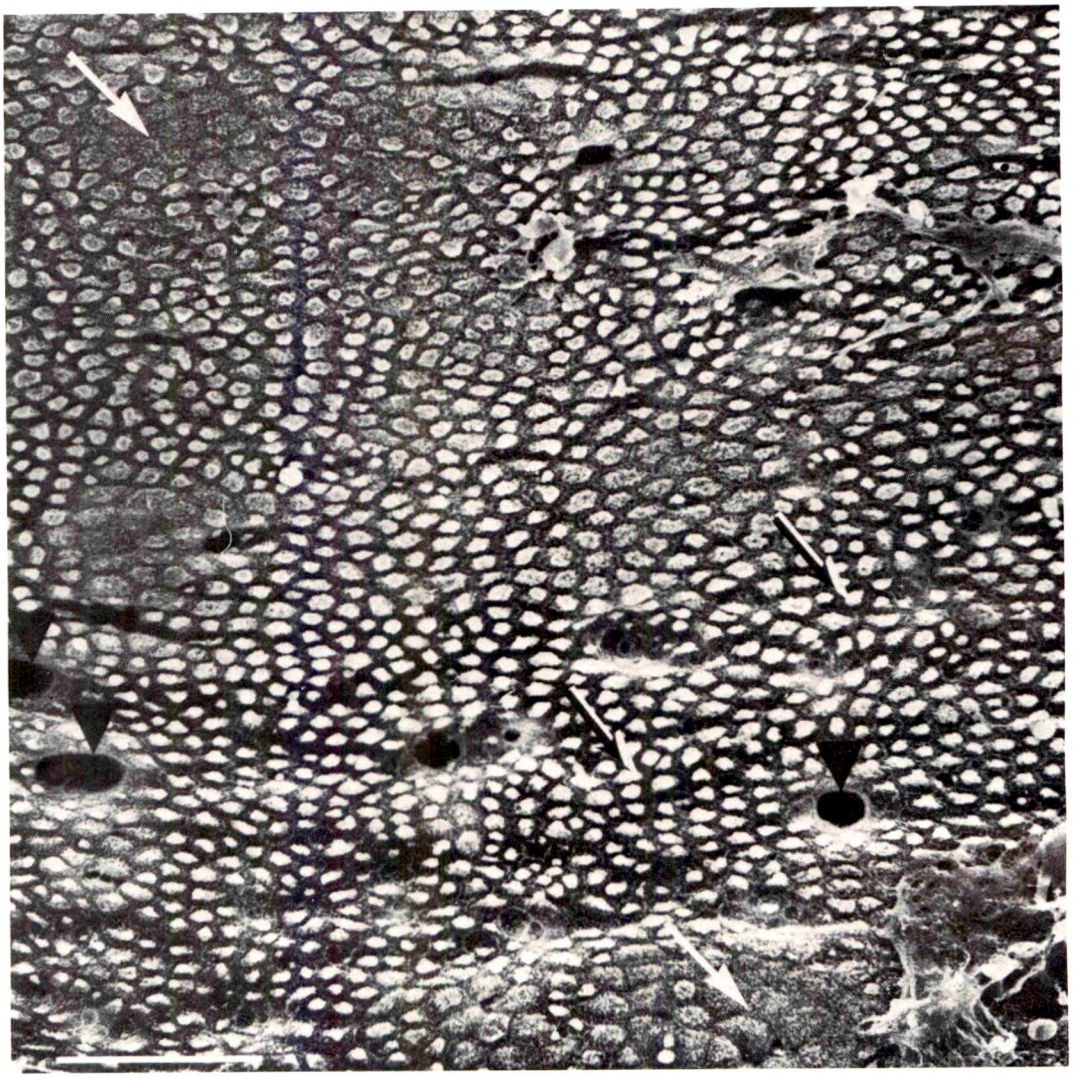


Fig. 2 (Greiner and associates). Micrograph of upper tarsal conjunctiva showing a range of cell surface changes, from areas of normal cells (white arrows) to highly abnormal cell surfaces (black-on-white arrows). Note mucus material (lower right corner) and crypts of Henle (black triangles) (bar gauge=30 μ; ×860).

(Figs. 7 and 8), which in some cells appeared to be covered by mucoidlike structures (Fig. 8). Unlike the mucus caps described as a preparation artifact in a previous study,[2] these coverings appeared to be intimately associated with the microvilli.

Although numerous altered cells were present in all asymptomatic lens wearers, the number of altered cells varied significantly in each specimen. No statistical analysis was conducted to determine the number of altered epithelial cells. However, we estimated that cell changes occupied 25 to 75% of the total specimen area.

Discussion

The most dramatic change in the surface anatomy of the upper tarsal conjunctiva among asymptomatic contact lens

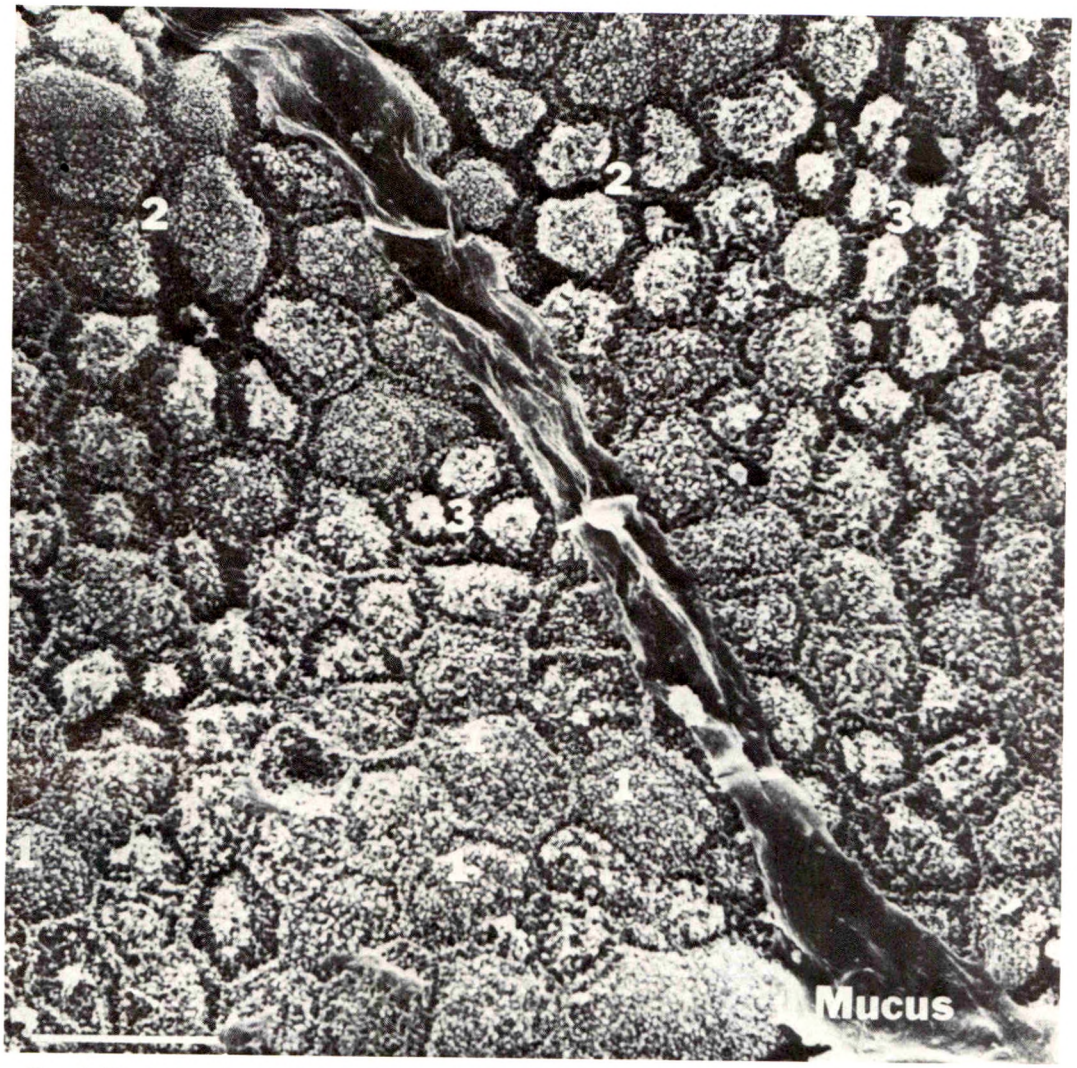


Fig. 3 (Greiner and associates). Conjunctival cell surface showing normal-appearing cells (1), mild centralization of microvilli away from cell borders (2), and extreme centralization of microvilli (3). Note mucus (bar gauge=10 μ; ×2,320).

wearers was the centralization of microvilli and the reduction of cell surface area. This combined phenomenon, which may indicate an adaptive mechanism of the cells in response to the contact lenses, seems to progress from a mild tendency of the microvilli to centralize, accompanied by a slight reduction in cell size, to an extreme centralization and a dramatic reduction in size (Figs. 5-8).

Cells with highly centralized microvilli were often covered by what appeared to be mucus, which may have been extruded from the cell onto the cell surface. These same changes were occasionally found in normal subjects. Takakusaki[4] showed that in normal conjunctiva, non-goblet cell epithelial cells can perform a secretory function. Perhaps the centralized microvillar form with associated mucus, in nor-

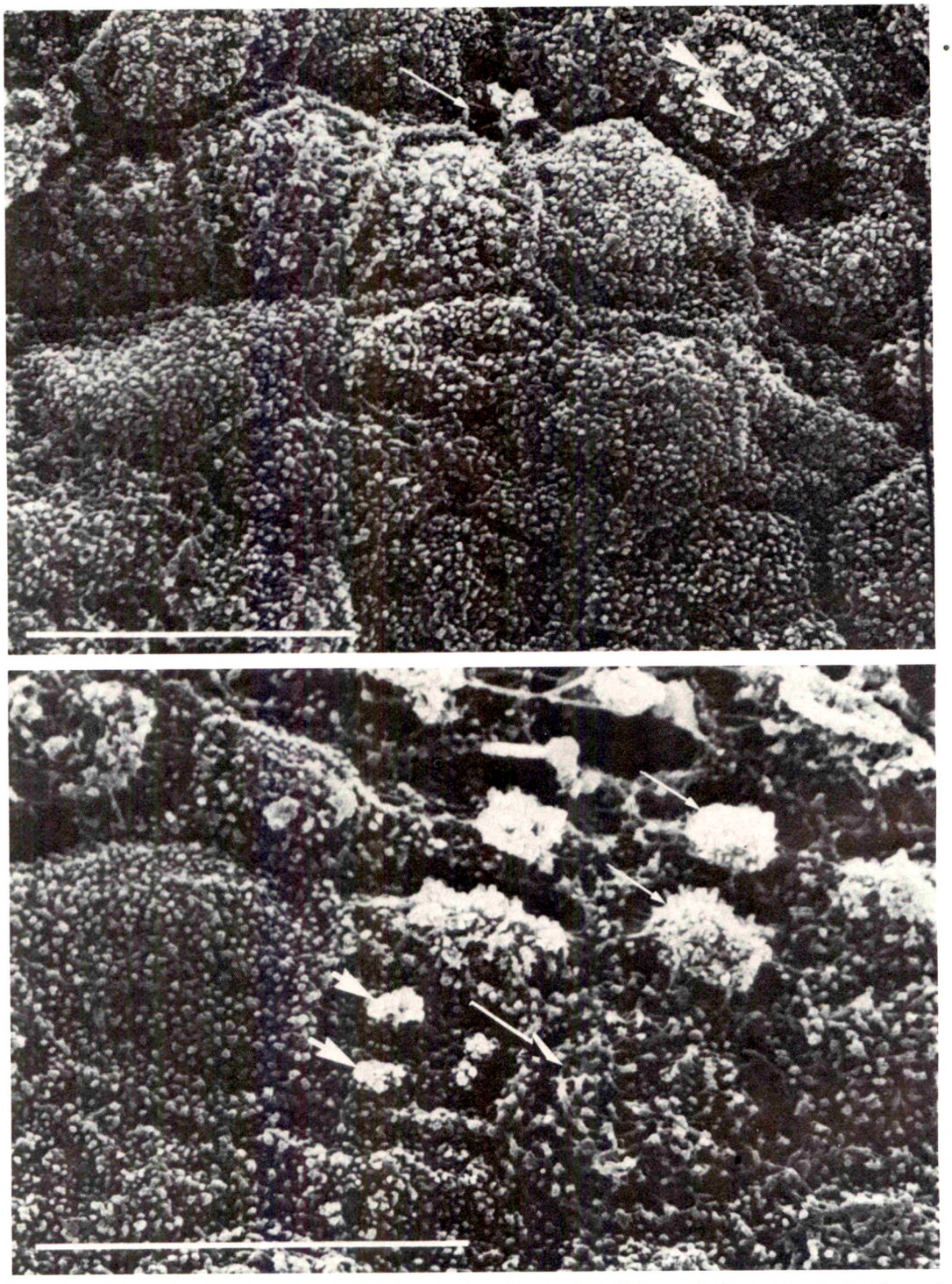


Fig. 4 (Greiner and associates). Top, Conjunctival surface and small intercellular crypt opening (arrow) with central, white particulate substance. Subtle tufted microvillar structures are present in some cells (arrowheads) (bar gauge=10 μ; ×4,710). Bottom, Conjunctiva showing normal epithelial cells with densely packed microvilli (left center), mild centralization of microvilli (black-on-white arrow), more extreme centralization (white arrows), and a cell with tufted microvillar structures (arrowheads) (bar gauge=10 μ; ×6,290).

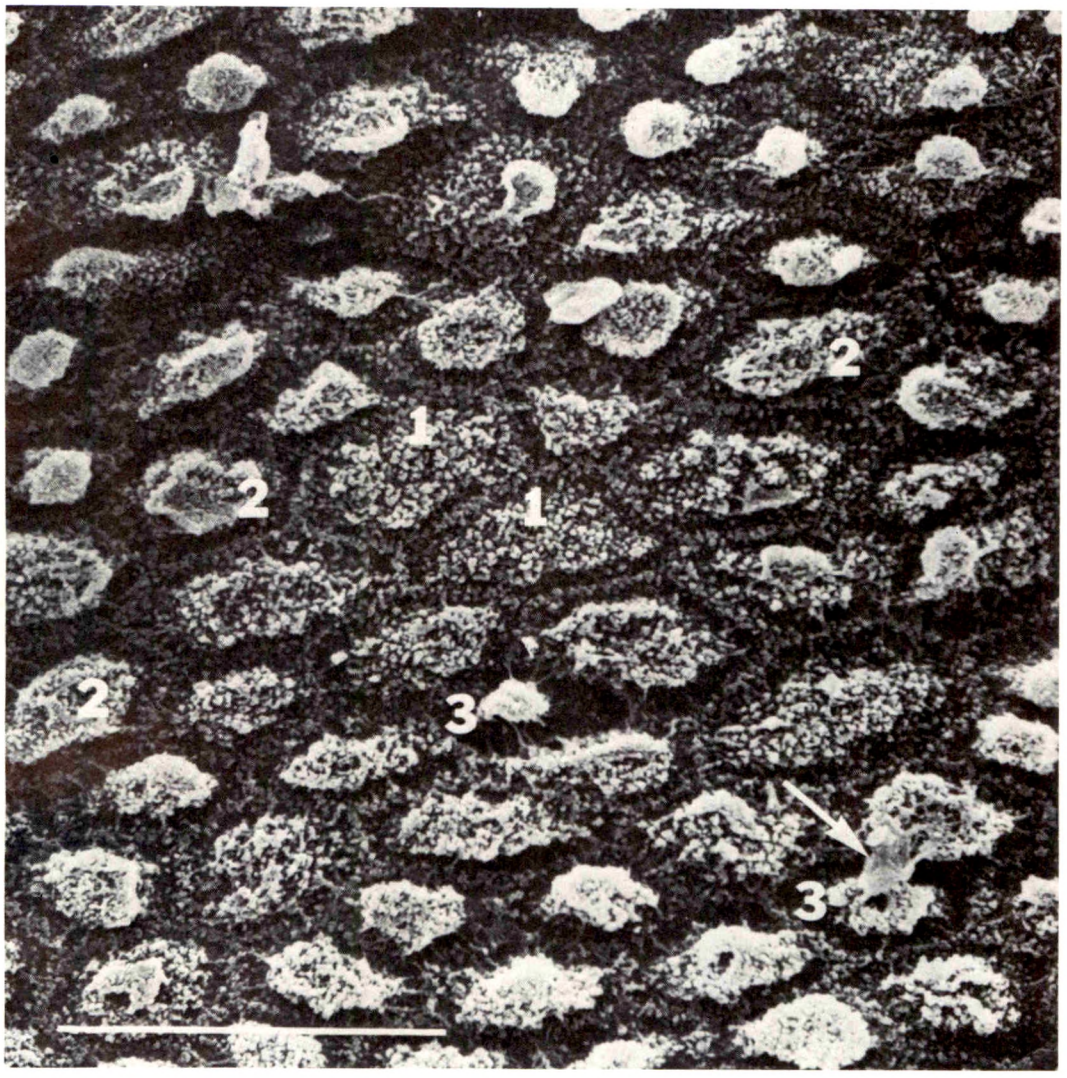


Fig. 5 (Greiner and associates). Conjunctiva with various degrees of centralization of microvilli: mild (1), moderate (2), extreme (3). Note mucus debris (arrow) and bared plasma membrane at cell periphery (bar gauge=10 μ; ×4,960).

mals and contact lens wearers, represents induction of a secretory process, and not trauma alone.

The upper tarsal conjunctival surface in asymptomatic contact lens wearers differed from that seen both in normal subjects[2] and in subjects with contact lens-associated giant papillary conjunctivitis.[3] However, the epithelial surface characteristics of the asymptomatic lens wearers bore certain similarities to both: (1) Normal epithelial cells were present in tissue from all groups, although these cells were scarce in subjects with giant papillary conjunctivitis. (2) Cells containing several tufted microvillar structures were seen in all groups, although members of both the asymptomatic and the normal group had few cells of this type, in contrast to the large number found in subjects with

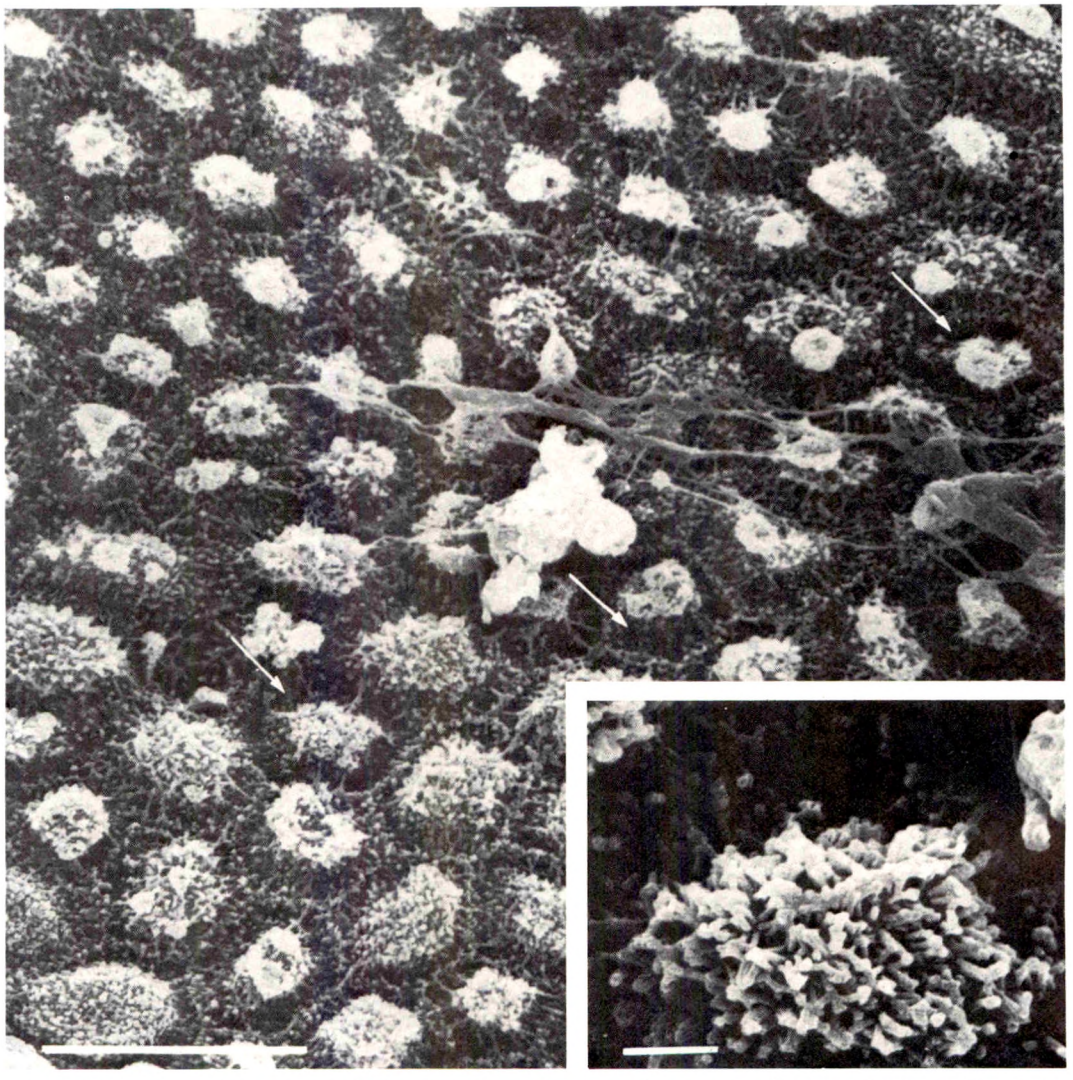


Fig. 6 (Greiner and associates). Epithelial cells with extremely centralized microvillar structures, some with peripheral plasma membrane that appears to be devoid of microvilli (arrows). Particulate and strand mucus is seen centrally (bar gauge=10 μ; ×3,390). Inset, High-power photomicrograph of centralized tuft of altered microvilli (bar gauge=1 μ; ×10,000).

giant papillary conjunctivitis.[3] (3) Small surface openings were seen in tissue from all three groups. They were uniform in normal subjects,[2] uniform to slightly irregular in the asymptomatic group, and highly irregular in subjects with giant papillary conjunctivitis.[3] (4) Crypts of Henle were seen both in asymptomatic and normal groups,[2] but not in subjects with giant papillary conjunctivitis.[3] (5) Centralized microvilli were seen commonly in the asymptomatic group, whereas this configuration appeared infrequently in normals.

Conjunctival epithelial cells in subjects with giant papillary conjunctivitis showed vast changes and distortion,[3] whereas similarly distorted cells were seldom seen in asymptomatic contact lens wearers. Such cellular morphology in

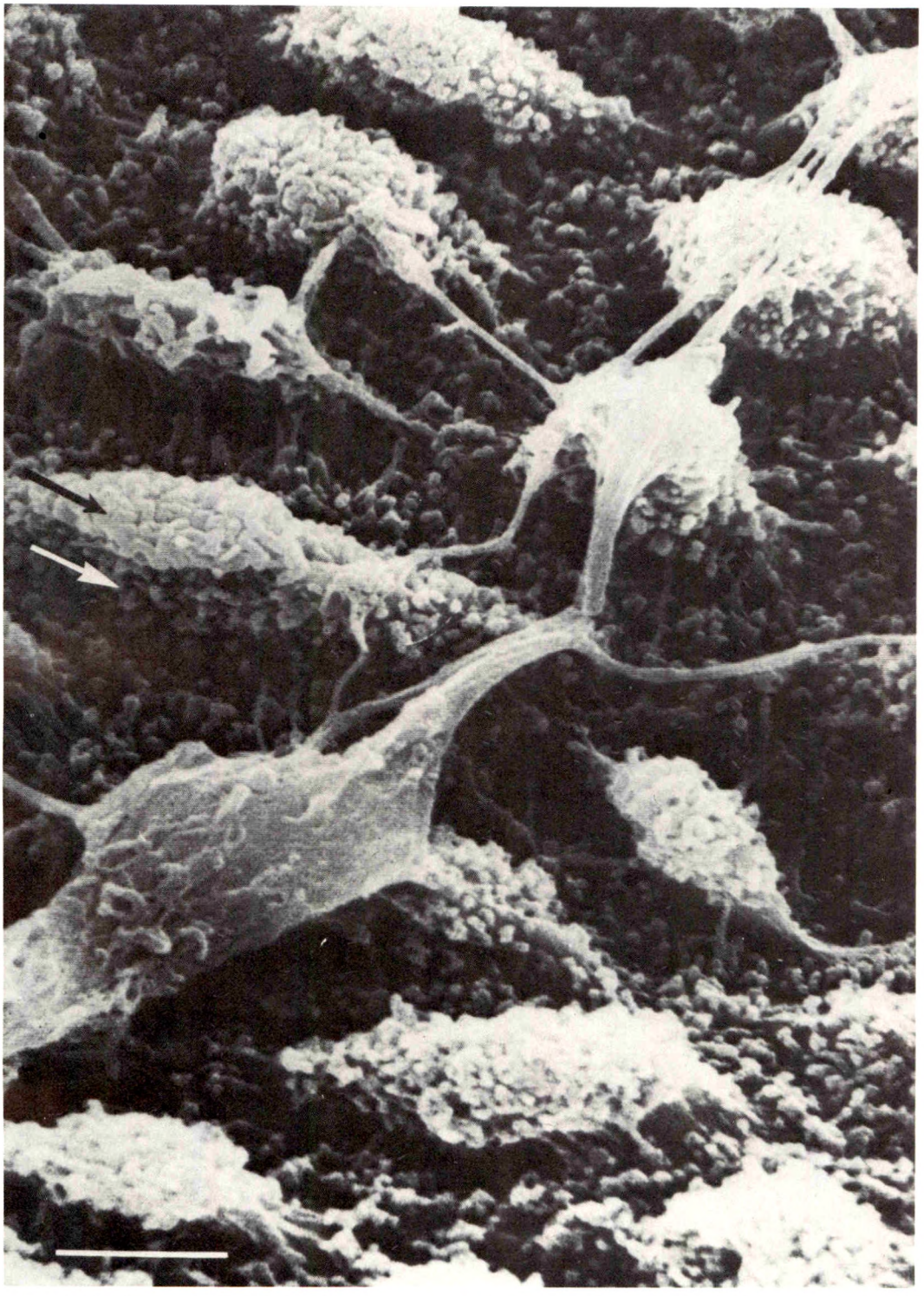


Fig. 7 (Greiner and associates). High-power photomicrograph of conjunctiva. Note coverings (black arrow) on centralized microvilli (white arrow). Mucus strands extend from one cell's microvilli to another (bar gauge=2 μ; ×12,220).

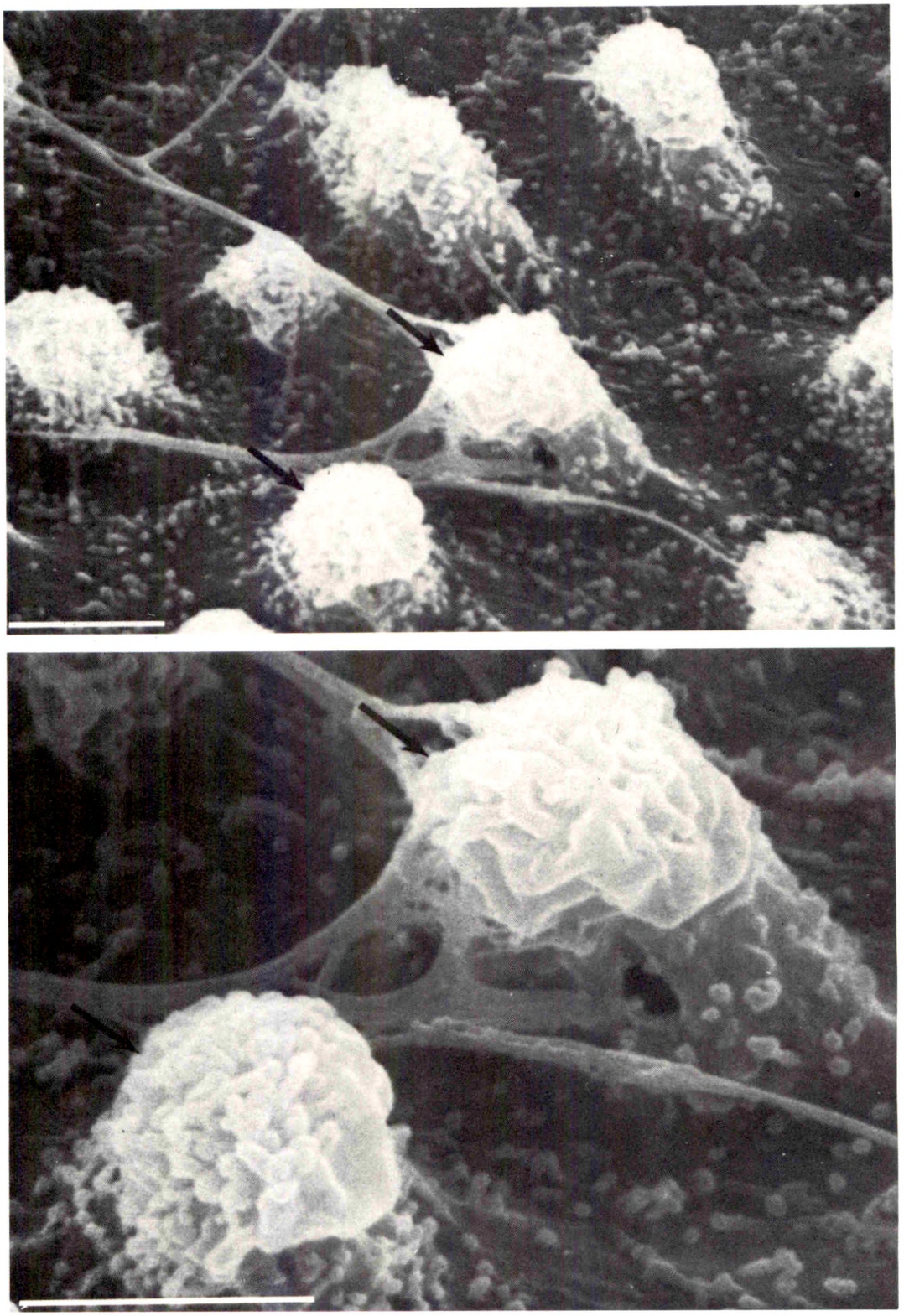


Fig. 8 (Greiner and associates). Top, Extremely centralized microvilli with covering of mucuslike material (arrows) (bar gauge=2 m; ×11,580). Bottom, High magnification of mucuslike covering over microvilli (arrows) (bar gauge=2 m; ×22,000).

giant papillary conjunctivitis may arise secondarily to stretching and elongation of cells and enormous growth of the tissue.

The trauma associated with contact lens wearing might induce either the epithelial changes characteristic of giant papillary conjunctivitis or, perhaps, some other epithelial alteration. If our investigation revealed that the conjunctiva was normal, that is, the same as that found in our group of normal subjects, then trauma could be excluded as a contributing factor to changes seen in contact lens-associated giant papillary conjunctivitis. All asymptomatic contact lens wearers studied showed surface changes in the biopsy specimens, which established that they did not have normal conjunctivae. Furthermore, all specimens revealed cells with alterations that were similar enough to assure us that these changes were typical, at least for these 11 subjects.

The number of altered cells in the biopsy specimens of the hard and soft asymptomatic contact lens wearers did not differ distinctly. However, the rigid and potentially more traumatic hard lens material might be responsible for a greater number of altered cells in hard, as compared to soft lens wearers, but no statistical analysis was done. Therefore, we were unable to rule out the role of trauma in inducing surface changes in giant papillary conjunctivitis, and must consider that the conjunctival changes in asymptomatic contact lens wearers might either result from trauma or the influence of early alterations in cellular mechanisms.

Because all 11 specimens from asymptomatic contact lens subjects were found to have altered conjunctival surfaces and all of them were both asymptomatic and without biomicroscopically visible ocular or upper tarsal conjunctival changes, considerable alterations of surface anatomy may occur without changes of function or induction of symptoms.

Summary

Biopsy specimens of the upper tarsal conjunctiva from 11 asymptomatic, biomicroscopically normal contact lens wearers (five hard and six soft) were studied by scanning electron microscopy. The conjunctiva in lens wearers showed areas of normal epithelial cell surfaces interspersed among areas of altered cells. The altered cell surfaces were characterized by centralized clumped microvilli and baring of that portion of the plasma membrane around the cell periphery. The degree of centralization of microvilli varied widely, from a mild tendency to centralize accompanied by slight reduction in cell diameter, to an extreme centralization and dramatic diameter reduction. In some cells, the centralized microvillar structure had a unique mucuslike covering.

Numerous altered cells were present in all 11 specimens from asymptomatic contact lens wearers. The number of these cells found by conjunctival biopsy of the hard contact lens wearers and the number in the soft contact lens wearers apparently did not differ.

The upper tarsal conjunctiva in these asymptomatic contact lens wearers has an altered epithelial surface, different from that observed in normal subjects without contact lens-wearing experience and from subjects with contact lens-associated giant papillary conjunctivitis.

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AN UNUSUAL CASE OF OPHTHALMOPLEGIC MIGRAINE

MARC P. CRUCIGER, M.D., AND MALCOLM L. MAZOW, M.D.

Houston, Texas

Although migraine is a common clinical entity in ophthalmologic and neurologic practice, ophthalmoplegic migraine (recurrent oculomotor palsy without demonstrable organic etiology) is rare. Since the first description in 1890, approximately 200 cases have been reported. According to Walsh and O'Doherty[1] most of these early cases should be excluded because the third nerve palsy was actually caused by aneurysm, infection, or tumor. With modern neuroradiologic techniques readily available, the reports of "ophthalmoplegic migraine" have markedly diminished as underlying structural pathology is found.

We present herein a case of ophthalmoplegic migraine in a 33-year-old man, which demonstrates some unusual features in duration and frequency of attacks.

CASE REPORT

A 33-year-old man was admitted on Aug. 4, 1976, to the emergency room of our hospital complaining of headache and diplopia. The headache had an abrupt onset, was throbbing, and was located in the frontal area without predilection for either side of the head. The patient complained of nausea and lightheadedness. As a child he had had headaches without visual aura or diplopia. His mother was migrainous. The patient had peptic ulcer disease and hemorrhoids. He denied smoking, drinking, or drug abuse.

Physical examination on admission revealed that he was an alert 33-year-old man with normal vital signs. His neurologic examination was normal except for a complete (internal and external) right oculomotor palsy.

To rule out an internal carotid-posterior communicating aneurysm, emergency cerebral angiography was performed. No abnormality was found.

Within one hour, the patient's symptoms of diplopia and headache were gone. Neurologic examination revealed a full recovery of the paretic oculomotor nerve except for a sluggish direct pupillary response and a residual anisocoria of 2 mm (right pupil larger than left). Further laboratory tests during the patient's hospitalization included an electroencephalogram, brain scan, sedimentation rate, complete blood cell count, and blood chemistries, all of which were normal. The patient was discharged without medication and was closely observed by the Neurology and Ophthalmology Services.

During the next 1½ years after discharge, the patient reported numerous episodes of headache and diplopia lasting one hour or less. These "attacks" occurred weekly and did not last for more than one hour. All symptoms and signs cleared except for a sluggish right pupillary response to direct light and a residual anisocoria. No third nerve misdirection was noted. One of us (M.P.C.) was able to observe one such attack and timed its duration at 46 minutes. The patient is shown during the episode of ophthalmoplegia (Fig. 1) and 45 minutes later (Fig. 2). During the attacks the patient exhibited no seizure-like activity.

The patient has been treated at appropriate dosage levels with up to 40 mg of propranolol HCl four times a day, 2 mg of ergotamine tartrate sublingually, and 4 to 8 mg per day of methysergide maleate for three weeks. None of these resulted in a cessation of frequency or duration of the attacks. The patient is still under close observation.

DISCUSSION

In 1890, Charcot[2] defined the syndrome of ophthalmoplegic migraine as "migraine associated with a third or other ocular palsy, which is transient at first but later may become permanent." For a case of ophthalmoplegic migraine to be diagnosed, other causes of headache with oculomotor palsy must be excluded. The advent of neuroradiologic procedures in 1930 underscored the rarity of ophthalmoplegic migraine as evidenced by the relative dearth of case reports from 1940 to the present (approximately 50 cases). The rarity of this clinical entity is emphasized by Friedman, Harter, and

From the University of Texas Medical School at Houston, Houston, Texas.

Reprint requests to Malcolm L. Mazow, M.D., 1121 Hermann Professional Bldg., Houston, TX 77030.

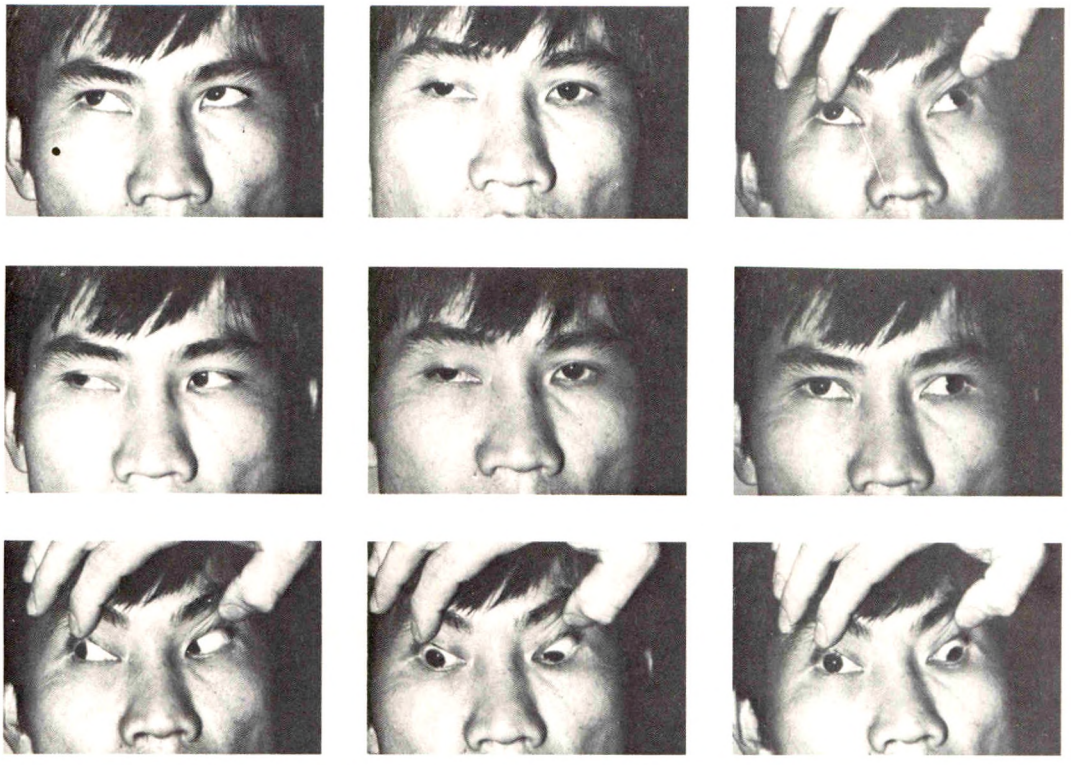


Fig. 1 (Cruciger and Mazow). Oculomotor palsy during headache.

Berritt,[3] who, in reviewing 5,000 cases of migraine seen at the Montefiore Hospital from 1932 to 1962, could only identify eight cases of ophthalmoplegic migraine.

From reports by Friedman, Harter, and Berritt,[3] Pearce,[4] Alpers,[5] Walsh,[1] Lincoff and Cogan,[6] Anderson,[7] and others[8–11,13] (Table), we have attempted to clarify this unusual syndrome and make some generalizations about it. The ophthalmoplegic migraine syndrome usually occurs first in childhood or young adulthood, although it can happen at any age and occurs as frequently in males as in females.[14] The headache is usually ipsilateral to the paretic nerve and generally precedes the paresis by several hours or days. Few studies report that the oculomotor palsy occurs concurrently with the headache; rather, it usually occurs immediately after the pain subsides. Internal and external paresis of the oculomotor nerve is common. The paresis usually lasts days to weeks and recovery is gradual and sometimes incomplete. Therapy has been unrewarding.[2,12,15]

The rarity of ophthalmoplegic migraine in itself merits study, and our case presents some additional unusual features. First, the patient's attacks of headache and ophthalmoplegia began and ended concurrently. Second, and even more unusual, his attacks were short, 45 minutes, and constant in duration. At no time did the patient report headache and diplopia lasting more than one hour. Finally, his attacks occurred weekly. No previous report has revealed a case of ophthalmoplegic migraine attacks occurring with such brevity and regularity.

TABLE

CHARACTERISTICS OF OPHTHALMOPLEGIC MIGRAINE

Case	No.	Age at Onset of First Attack (yrs)	Pain		Onset of 3rd Nerve Palsy Relative to Pain	3rd Nerve Palsy		Duration of 3rd Nerve Palsy	Arteriorgram	Prior History of Headaches	No. of Attacks
			Ipisilateral to 3rd Nerve Palsy	Duration		Internal	External				
Saundby[8] (1882)	1	12	Yes	5 days	Later	Yes	Yes	Wks	3	No	2
Nason[9] (1891)	1	7	Yes	24 hrs	Later	Yes	Yes	24-48 hrs	3	Yes	Multiple
Finlay[10] (1907)	1	22	Yes	4 days	Later	Yes	Yes	3 wks	3	Yes	1
Townsend[11] (1930)	1	22	?	?	Later	No	Yes	2 mos	3	Yes	3
Alpers and Yaskin[5] (1951)	1	52	Yes	24-48 hrs	Concurrent	No	Yes	Wks	Negative	Yes	3
	2	23	No	4-5 hrs	Concurrent	Yes	Yes	4 hrs-days	Negative (Narrow internal carotid)	Yes	2(died of thrombosis of internal carotid artery after arteriogram)
Verbruggen[13] (1955)	1	14 mos	No (frontal)	Hrs	12 hrs later	No	Yes	4-6 wks	Negative (Narrow) internal carotid)	No	12
Lincoff[6] (1957)	1	11	Yes	11 days	Concurrent	Yes	Yes	1 mo	Normal	Yes	1
	2	2	Yes	10 days	Concurrent	Yes	Yes	5 days	Normal	No	15
Walsh, J.[1] (1960)	1	23	Yes	2 wks	8 hrs later	Yes	Yes	2 mos	Negative*	Yes	2
	2	19	No	2 days	Later	No	Yes	1 mo	Negative*	Yes	10
	3	12	Variable	Days	Concurrent	No	Yes	Days	Negative*	No	3
Friedman, Harter, and Berritt[3] (1962)	1	9	Yes	4 days	Later	Yes	Yes	3 wks	Normal	Yes	3
	2	2	Yes	24-48 hrs	Later	Yes	Yes	7 days	Normal	No	5
	3	3	Yes	4 days	Later	Yes	Yes	7 days	Normal	No	20
	4	3	Yes	2 days	Later	Yes	Yes	3 days	Normal	Yes	3
	5	8	Diffuse frontal	3 days	Concurrent	No	Yes	7 days	Normal	Yes	1
	6	17	Yes	4-5 days	Later	Yes	Yes	Days to wks	Normal	No	5
	7	5	Yes	3 days	Later	Yes	Yes	14 days	Normal	Yes	5
	8	30	Yes	20 days	Later	Yes	Yes	30 days	Normal	Yes	20
Pearce[2] (1968)	1	41	Yes	2-4 days	24 hrs later	Yes	Yes	14 days	Normal	Yes	20
	2	33	Yes	?	Concurrent	Yes	Yes	4 wks	Normal	Yes	1
	3	28	?	?	Concurrent	No	Yes	4-7 days	Not done	Yes	3
	4	16	Yes	Hrs	Concurrent	?	Yes	3-5 wks	Normal	Yes	?
	5	42	?	?	Later	No	Yes	24-hrs-mos	Normal	Yes	3
	6	51	?	48 hrs	24 hrs later	No	Yes	1 mo	Normal	Yes	3
Anderson[7] (1974)	1	3	Diffuse	2 days	Later	Yes	Yes	3 wks	-	No	2
	2	20	Yes	?	Later	Yes	Yes	3-5 wks	-	Yes	8
Present study	1	33	Diffuse	45 min	Concurrent	Yes	Yes	45 min	Negative	Yes	50

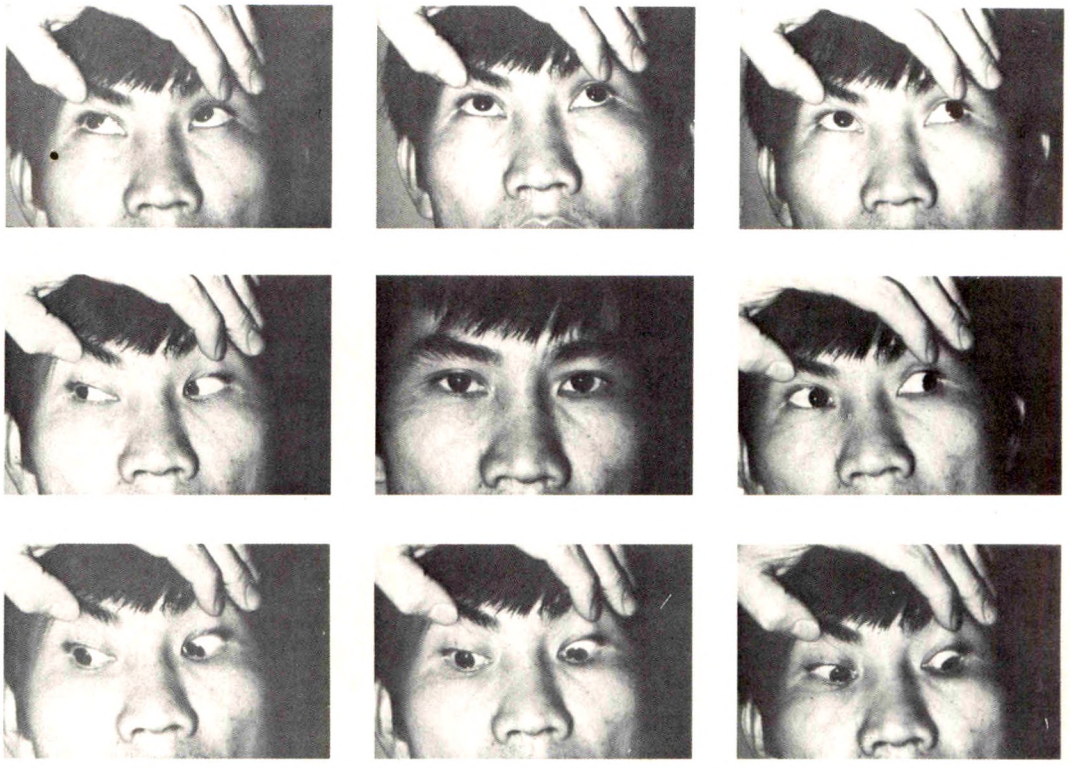


Fig. 2 (Cruciger and Mazow). Normal motility 45 minutes after onset of headache.

Summary

A 33-year-old man complaining of headache and diplopia lasting one hour or less and occurring weekly was found to have ophthalmoplegic migraine. He was treated unsuccessfully with propranolol HCl, ergotamine tartrate, and methysergide maleate.

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EVALUATION OF DEXAMETHASONE ACETATE AS A TOPICAL OPHTHALMIC FORMULATION

HOWARD M. LEIBOWITZ, M.D., AND ALLAN KUPFERMAN, PH.D.
Boston, Massachusetts

AND

ROBERT H. STEWART, M.D., AND RICHARD L. KIMBROUGH, M.D.
Houston, Texas

Alteration of the derivative of a corticosteroid base alters its pharmacologic behavior when the compound is administered topically to the eye.[1] Experimental studies of commercially available ophthalmic prednisolone preparations demonstrated the superiority of the acetate derivative as an anti-inflammatory agent.[2,3] Ophthalmic dexamethasone preparations also are widely used. Although this corticosteroid base is commercially available as a free alcohol and as a phosphate derivative, it is not available as an acetate derivative for topical ophthalmic use. The superiority of this derivative of prednisolone prompted us to investigate a comparable formulation of dexamethasone.

MATERIAL AND METHODS

We performed all studies on both sexes of New Zealand albino rabbits weighing between 1.5 and 2.0 kg. The animals were not anesthetized during the administration of the drug. For the bioavailability studies, we used a corticosteroid preparation of micronized 0.1% suspension of tritiated dexamethasone acetate. The corticosteroid was general-labeled and had a specific activity of 22.68 μCi/mg. For the animal studies of therapeutic efficacy and the human studies of corticosteroid–induced intraocular pressure increase, we used an identical, nonradioactive labeled 0.1% suspension of dexamethasone acetate.

The techniques for measuring the amount of corticosteroid entering the cornea and aqueous humor have been described in detail.[4] Briefly, the animals were divided into three groups as follows: (1) intact corneal epithelium, no ocular inflammation; (2) corneal epithelium removed, no ocular inflammation; and (3) intact corneal epithelium, intraocular inflammation. A standard 0.05-ml drop of the radioactive-labeled dexamethasone acetate was placed on the center of the corneal surface of both eyes. The eyelids were blinked manually three times and closed with masking tape. An overdose of intravenously administered pentobarbital sodium at fixed times after corticosteroid administration killed the animals. Aqueous humor samples were aspirated from the anterior chamber with a 25-gauge needle attached to a tuberculin syringe. A standard 8-mm central corneal sample was obtained for analysis by trephination. The corneal and aqueous humor samples were solubilized, and corticosteroid levels in the samples were determined by scintillation counting techniques.

The ability of 0.1% dexamethasone acetate to suppress inflammation in the cornea also was measured as described previously.[2,5] Corneal inflammation was

From the Boston University School of Medicine Departments of Ophthalmology (Drs. Leibowitz and Kupferman) and Pharmacology (Dr. Kupferman), Boston, Massachusetts; and the University of Texas Health Science Center, Connor Glaucoma Center (Drs. Stewart and Kimbrough), Houston, Texas. This study was supported in part by Public Health Service Grant EY00544 from the National Eye Institute (Dr. Leibowitz), and grants from the Massachussets Lions Eye Research Fund, Inc., and from Research to Prevent Blindness, Inc.

Reprint requests to H. M. Leibowitz, M.D., Boston University School of Medicine, 80 East Concord St., Boston, MA 02118.

produced by the injection of clove oil directly into the corneal stroma. Histologically, the reaction is characterized by polymorphonuclear leukocytic infiltration of the stroma. Before the induction of the keratitis, the polymorphonuclear leukocytes were systemically radioactive labeled by the intravenous administration of tritiated thymidine. Twenty-four hours after the induction of corneal inflammation, therapy was initiated. The regimen consisted of a standard drop (0.05 ml) of drug administered hourly for a total of six doses, and then, 18 hours later, one drop was administered hourly for an additional total of seven doses. Standardized corneal samples obtained by trephination were then solubilized and their level of radioactivity was measured by scintillation counting techniques. The decrease in corneal radioactivity, which is proportional to the decrease in labeled polymorphonuclear leukocytes, provides an objective determination of corticosteroid anti-inflammatory effectiveness.

Eight individuals who had previously been treated with dexamethasone sodium phosphate 0.1% and who were known to be corticosteroid responders volunteered as subjects for the evaluation of dexamethasone acetate. On a regimen of one drop of dexamethasone sodium phosphate four times daily, each of the subjects had an intraocular pressure increase of more than 10 mm Hg in the treated eye only. At least two months without corticosteroid administration elapsed before the subjects were given dexamethasone acetate. The intraocular pressure returned to normal levels during this interval in each instance.

The subjects instilled one drop of the 0.1% dexamethasone acetate suspension into one eye only four times a day. We measured their intraocular pressure by applanation tonometry at weekly intervals for six weeks. Whenever the intraocular pressure in the treated eye increased more than 10 mm Hg above the baseline value, the subject was removed from the study and the dexamethasone acetate drops were discontinued. Following discontinuation of the corticosteroid, intraocular pressure returned to normal in all cases.

Results

In each of the three groups of experimental animals studied, peak corticosteroid levels in the cornea were achieved within the first five minutes after the drug was applied and remained stationary for the subsequent hour (Table 1). By the second hour after drug administration, however, corticosteroid levels in the cornea were significantly less ($P<.05$). The pattern in the aqueous humor was considerably different. In each of the three groups of experimental animals, aqueous humor corticosteroid levels rose progressively, reaching a peak 60 minutes after instillation of dexamethasone acetate suspension and decreasing significantly ($P<.05$) in the subsequent hour.

Calculation of the area under the drug concentration vs time curve for both cornea and aqueous humor, a measure of the drug's bioavailability in each location, produced data that paralleled our observations on peak corticosteroid levels. The total quantity of dexamethasone acetate present in the cornea and aqueous humor did not differ significantly ($P>.05$) in the three experimental situations we investigated (Table 2).

Topically applied dexamethasone acetate effectively suppressed an experimental inflammatory keratitis. Treatment with this agent produced a 54.6% mean decrease in the numbers of labeled polymorphonuclear leukocytes invading the cornea with an intact epithelium and a 59.9% reduction in these inflammatory cells when the epithelium was absent (Table 3).

The intraocular pressure of six of the

TABLE 1

CONCENTRATION OF DEXAMETHASONE ACETATE IN CORNEA AND AQUEOUS HUMOR*

Time after Drug Administration (min)	Group 1†	Group 2‡	Group 3§
		CORNEA	
5	1.75 (± 0.19)	0.99 (± 0.16)	0.98 (± 0.15)
15	1.40 (± 0.17)	1.08 (±).19)	1.00 (± 0.19)
30	1.51 (± 0.28)	0.91 (± 0.17)	0.96 (±).20)
60	1.05 (± 0.11)	0.87 (±).19)	0.71 (±).14)
120	0.67 (±).09)	0.41 (±).06)	0.23 (± 0.08)
		AQUEOUS HUMOR	
5	0.034 (± .003)	0.031 (± .002)	0.030 (± .001)
15	0.042 (± .007)	0.036 (± .006)	0.032 (± .008)
30	0.097 (± .012)	0.079 (± .010)	0.065 (± .011)
60	0.136 (± .038)	0.111 (± .024)	0.099 (± .020)
120	0.081 (± .021)	0.061 (± .020)	0.060 (± .031)

*Following topical administration of 0.05 ml of 0.1% tritiated dexamethasone acetate (specific activity 22.68 μCi/mg). Table entries are the arithmetic mean ± the standard error of the mean of data derived from the study of six eyes (three animals).
†Epithelium intact, uninflamed eye.
‡Epithelium removed, uninflamed eye.
§Epithelium intact, inflamed eye.

eight subjects studied increased 10 mm Hg or more during the six weeks of treatment with dexamethasone acetate. The intraocular pressure of the remaining two subjects increased by 9 mm Hg. Direct comparison of this effect with that measured after instillation of dexamethasone sodium phosphate in the same subjects failed to demonstrate any difference in the degree of intraocular pressure increase (Table 4).

TABLE 2

TOTAL CONCENTRATION WITH TIME OF CORTICOSTEROID IN THE RABBIT CORNEA AND AQUEOUS HUMOR FOLLOWING TOPICAL ADMINISTRATION OF 0.05 ML OF 0.1% TRITIATED DEXAMETHASONE ACETATE

Group	Cornea (μg-min/g)	Aqueous Humor (μg-min/ml)
1—Epithelium intact, uninflamed eye	175	14
2—Epithelium removed, uninflamed eye	118	12
3—Epithelium intact, inflamed eye	111	10

DISCUSSION

The present experiments confirm our previous observations that a change in the derivative of a corticosteroid base alters its pharmacological behavior in the eye.[1,6] In previous studies of dexamethasone sodium phosphate[4] and of dexamethasone alcohol,[7] we found that the quantity of drug that gains access to the cornea and aqueous humor varies greatly, depending on whether the corneal epithelium is intact or absent and on whether or not the eye is inflamed. However, these factors do not appear to have a major effect on the ocular bioavailability of topically instilled dexamethasone acetate. The amount of dexamethasone acetate that could be measured in the cornea and aqueous humor was essentially the same regardless of the status of the corneal epithelium

TABLE 3

MEAN DECREASE IN CORNEAL INFLAMMATORY ACTIVITY FOLLOWING TOPICAL ADMINISTRATION OF 0.1% DEXAMETHASONE ACETATE*

Treatment	Epithelium Intact	Epithelium Removed
0.05 ml once an hour, six times a day 24 hours after induction of inflammation, then lapse of 18 hours, then 0.05 ml once an hour, seven times a day	54.6 (± 8.0)	59.9 (± 6.9)

*Table entries are the arithmetic mean ± the standard error of data derived from the study of 12 eyes (six rabbits). Values are expressed as the percentage difference from the mean of 12 untreated control eyes (six rabbits).

or the presence or absence of intraocular inflammation. Moreover, the total quantity of drug measured in the cornea and aqueous humor, under each of the experimental conditions studied, was significantly less when dexamethasone acetate 0.1% was applied to the eye than when either dexamethasone alcohol 0.1% or dexamethasone sodium phosphate 0.1% was administered (Table 5).

Similarly, the ability of each of these dexamethasone derivatives to suppress inflammation in the cornea is substantially different.[8] In contrast to the bioavailability values, dexamethasone acetate is the most effective therapeutic agent of the three derivatives studied. Taken together, the bioavailability and efficacy data indicate that dexamethasone acetate is not only the most effective of the three dexamethasone products, but also the most potent. That is, a unit amount of dexamethasone acetate in the cornea produced a greater anti-inflammatory effect than a

TABLE 4

INTRAOCULAR PRESSURE RESPONSE TO TOPICAL APPLICATION OF DEXAMETHASONE DERIVATIVES IN KNOWN CORTICOSTEROID RESPONDERS

					Dexamethasone Acetate			Dexamethasone Phosphate		
Patient No.	Age (yrs)	Sex	Race	Treatment Eye	Baseline (mm Hg)	Maximum Increase (mm Hg)	No. of Days Treated	Baseline (mm Hg)	Maximum Increase (mm Hg)	No. of Days Treated
1	68	M	W	L.E.	18	+13	42	18	+13	42
2	28	F	W	R.E.	21	+12	21	22	+11	21
3	67	F	W	L.E.	21	+19	21	21	+17	20
4	67	F	B	R.E.	18	+17	14	23	+14	42
5	50	M	B	R.E.	27	+26	34	26	+14	30
6	49	M	B	L.E.	16	+ 9	42	18	+11	42
7	54	F	W	R.E.	26	+ 9	42	22	+22	56
8	58	M	W	L.E.	15	+10	21	20	+20	38
					*20.250 ± 4.3	*14.375 ± 5.950		*21.250 ± 2.659	*15.250 ± 4.062	

*Mean (± S.D.).

TABLE 5

TOTAL CONCENTRATION WITH TIME OF CORTICOSTEROID IN THE RABBIT CORNEA AND AQUEOUS HUMOR FOLLOWING TOPICAL ADMINISTRATION OF VARIOUS DEXAMETHASONE DERIVATIVES

	Dexamethasone Acetate 0.1%	Dexamethasone Alcohol 0.1%	Dexamethasone Sodium Phosphate 0.1%
		CORNEA (μg-min/g)	
Epithelium intact uninflamed eye	175	452	0
Epithelium removed uninflamed eye	118	1,361	4,642
Epithelium intact inflamed eye	111	543	1,068
		AQUEOUS HUMOR (μg-min/ml)	
Epithelium intact uninflamed eye	14	43	0
Epithelium removed uninflamed eye	12	163	657
Epithelium intact inflamed eye	10	35	143

comparable amount of dexamethasone alcohol or dexamethasone sodium phosphate (Table 6).

Both of the commercially available ophthalmic dexamethasone derivatives, dexamethasone alcohol and dexamethasone sodium phosphate, can cause an increase in intraocular pressure in susceptible individuals.[9-12] Dexamethasone acetate shares this undesirable property. In two instances (patients No. 4 and No. 8, Table 4), the pressure increase occurred earlier following administration of the acetate derivative than it had with the phosphate derivative. However, the two dexamethasone derivatives caused this side effect in essentially the same manner and to the same degree. Unfortunately, the number of cases available to us for study failed to provide a definitive answer regarding the relative proclivity of these drugs to increase intraocular pressure in susceptible individuals. Additional longer term investigations are needed to settle this point conclusively. Nonetheless, our initial results suggest that dexamethasone

TABLE 6

ANTI-INFLAMMATORY POTENCY IN THE CORNEA OF TOPICALLY ADMINISTERED DEXAMETHASONE DERIVATIVES

	Anti-inflammatory Effectiveness (%)	Corneal Bioavailability (μg-min/g)
Epithelium intact		
Dexamethasone acetate 0.1%	54.6	111
Dexamethasone alcohol 0.1%	39.9	543
Dexamethasone sodium phosphate 0.1%	18.7	1,068
Epithelium absent		
Dexamethasone acetate 0.1%	59.9	118
Dexamethasone alcohol 0.1%	41.8	1,316
Dexamethasone sodium phosphate 0.1%	22.4	4,642

acetate is superior to the commercially available dexamethasone preparations for use as a topical ophthalmic anti-inflammatory agent.

Summary

Penetration of an ophthalmic suspension of 0.1% dexamethasone acetate into the rabbit cornea and aqueous humor was unaffected by the status of the corneal epithelium or by the presence or absence of intraocular inflammation. However, the total quantity of this corticosteroid that could be measured in the cornea or aqueous humor was significantly less than that produced by either dexamethasone alcohol or dexamethasone sodium phosphate. Despite this, dexamethasone acetate was the most effective of the three dexamethasone derivatives in suppressing inflammation in the cornea, which indicates that following topical administration to the eye it is the most potent of the dexamethasone derivatives studied.

This greater therapeutic effect does not seem to be accompanied by a greater propensity to increase intraocular pressure. Comparison of the intraocular pressure-increasing effect in known corticosteroid responders of dexamethasone acetate with that of dexamethasone sodium phosphate, the least effective of the dexamethasone products studied, demonstrated no difference between the two drugs. These data support the conclusion that dexamethasone acetate is superior to the commercially available dexamethasone derivatives for use as a topical ocular anti-inflammatory agent.

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NOTES, CASES AND INSTRUMENTS

ACUTE POSTERIOR MULTIFOCAL PLACOID PIGMENT EPITHELIOPATHY

RICHARD E. HECTOR, M.D.
San Francisco, California

Acute posterior multifocal placoid pigment epitheliopathy was first described by Gass[1] in 1968 as a unique syndrome that involved a rapid decrease in visual acuity and the appearance of multiple flat, yellowish white lesions in the posterior retina, followed by visual recovery in three to five months. The etiology of the syndrome has been elusive, although various infectious agents have been suspected. Of the three cases originally reported by Gass,[1] two patients had a positive tuberculin skin test and the third had a family history of tuberculosis. Other case reports have noted the onset of visual symptoms one to two weeks after an influenza-like illness.[2–4] One author[5] implicated adenovirus 5. We herein report the case of a patient who had the typical visual and ophthalmoscopic changes associated with acute posterior multifocal placoid pigment epitheliopathy following a mild hypersensitivity reaction to the swine flu vaccine.

From the Ophthalmology Service, Department of Surgery, Letterman Army Medical Center, Presidio of San Francisco, San Francisco, California.

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Reprint requests to Technical Publications Editor, Letterman Army Medical Center, Presidio of San Francisco, San Francisco, CA 94129.

CASE REPORT

On Nov. 24, 1976, a 21-year-old healthy man was inoculated with Victoria A and B and swine attenuated viruses. During the next 48 hours, he developed a low-grade fever, chills, headache, and blurred vision. During the next five days, the symptoms cleared except for the headache and blurred vision in both eyes. The patient was first seen by an optometrist who recorded his visual acuity at 6/12 (20/40) bilaterally. He was referred to an ophthalmologist who noted multiple flat, yellowish white lesions in the posterior pole of both eyes. The patient was then referred here for consultation and fluorescein angiography. Ophthalmoscopic examinations done at this time confirmed that the positive ocular findings were restricted to the retinal pigment epithelium of the posterior pole in both eyes. Examinations of the peripheral retinas, anterior segment, and intraocular pressures were unremarkable. Visual fields were within normal limits except for a small supracentral scotoma in the right eye. Angiographic studies done in December 1976 revealed multiple transmission defects throughout the posterior pole of both eyes, with areas of hypofluorescence followed by late hyperfluorescence, but no leakage.

Serology for viral antibody titers and cultures of cerebral spinal fluid were within normal limits. Electroretinograms done late in the examination were normal. Routine laboratory tests all showed normal values. Tuberculin skin tests were negative. Skin tests using the various components of the vaccines resulted in immediate and delayed reactions to the attenuated swine virus. We concluded that the patient had experienced a mild hypersensitivity reaction to the vaccination, which included the flu-like symptoms and the retinal pigment epithelium changes not unlike those described as occurring with acute posterior multifocal placoid pigment epitheliopathy. I observed the patient over a period of six months, during which his visual acuity improved to 6/6 (20/20) bilaterally. Ophthalmoscopic examinations revealed partial resolution of the pale placoid lesions with pigment clumping in and around these lesions. Repeat fluorescein angiograms failed to reveal any leakage of retinal vessels or choroidal filling abnormalities, but showed scattered lesions of hypo- and hyperfluorescence corresponding to the retinal pigment epithelium changes.

DISCUSSION

Gass[1] chose the term "epitheliopathy" because the three cases he reported in

1968 revealed minimal changes in the adjacent choroidal and retinal tissues that appeared to be secondary to the cloudy swelling of the pigment epithelial cells. Since then, at least 34 cases have been reported in this country. The epitheliopathy is usually bilateral and has almost equal sex distribution. Patients range in age from 8 to 57 years, and approximately 80% have a final visual acuity of 6/12 (20/40) or better. Recurrences have been reported.

Retinal pigment epithelium changes often have been suspected to be secondary to an infectious agent, or to a patient's hypersensitivity to one.[3] Scuderi, Recupero, and Valvo[8] proposed that the epitheliopathy is an early or mild form of a more generalized exudative retinitis and they reported similar retinal pigment epithelium lesions with signs of anterior uveitis (six cases) and posterior uveitis (two cases).[7] Scuderi, Recupero, and Valvo[8] believe that the 13 patients they have seen since 1948 with ophthalmoscopic lesions similar to those described by Gass[1] have progressed to more severe forms of uveal inflammation, retinoschisis, and retinal detachment. The occurrence of acute posterior multifocal placoid pigment epitheliopathy after bilateral serous detachments has also been reported.[9]

Because the epitheliopathy described by Gass[1] has proven to be self-limited with a generally good prognosis, no pharmacologic therapy is indicated. Approximately one third of the reported cases of acute posterior multifocal placoid pigment epitheliopathy have been treated with corticosteroids and failed to show any change in the course or the prognosis of the disease. Additionally, the use of these anti-inflammatory agents has been associated with recurrences of poor vision.[2] Our patient had no signs or symptoms of an anterior or posterior uveitis or central nervous system inflammation, although he was never treated with corticosteroids.

Summary

A 21-year-old man developed blurred vision and retinal pigment epithelium changes similar to those in acute posterior multifocal placoid pigment epitheliopathy following vaccination for swine flu. The patient's medical examination revealed no infectious agents. A hypersensitivity to the attenuated virus of the swine flu vaccine appears to have produced his initial flu-like symptoms and retinal pigment epithelium changes.

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AN INSERTION SLEEVE FOR PARS PLANA INFUSION PORTS

GEORGE W. BLANKENSHIP, M.D.
AND
WILLI AUMAYR
Miami, Florida

In pars plana vitreous surgery it is sometimes desirable to have a separate source of vitreous cavity infusion fluid, and it is mandatory with some instruments.[1] Inserting the infusion port is often difficult because of the small size of the port, the desirability of a tight fit, and the lack of a good instrument to grasp the port. The shaft of a 10-gauge hypodermic needle, or a 3-cm length of a 10-gauge stainless steel tubing can be modified to make an insertion sleeve and minimize these difficulties.

Two shallow slots the size of the infusion port wings are filed into the opposite sides of one end of a 3-cm length of 10-gauge tubing, or the shaft of a 10-gauge hypodermic needle after the beveled tip and Luer hub have been removed. The Luer hub of the infusion port silicone tubing is temporarily removed, and the tubing is passed through the inserter sleeve (Fig. 1) so that the slots can fit around the infusion port wings (Fig. 2). The infusion port silicone tubing is then reattached to its Luer hub.

The infusion port with its silicone tubing passing through the inserter sleeve can be gas-sterilized or autoclaved. At surgery the sclera and pars plana are appropriately perforated, and a fixation mattress suture is placed around the scleral perforation. The insertion sleeve is advanced so that its slots fit around the infusion port wings, and the port is inserted by pushing the sleeve with a twisting motion. The sleeve is then retracted

From the Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Florida.

Reprint requests to George W. Blankenship, M.D., 900 N.W. 17th St., Miami, FL 33152.

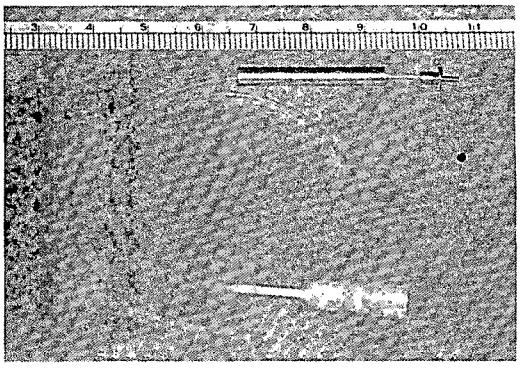


Fig. 1 (Blankenship and Aumayr). The silicone tubing of the pars plana infusion port passes through the inserter sleeve.

onto the silicone tubing, and the port is secured with the fixation suture. At the end of surgery, the infusion port is removed with forceps after the fixation has been cut, and the scleral perforation is closed with a suture.

SUMMARY

To facilitate placing pars plana infusion ports, we modified the shaft of a piece of 10-gauge tubing or of a hypodermic needle by removing the beveled tip and Luer hub, passing the tubing through the inserter sleeve, and then reattaching the tubing to the Luer hub.

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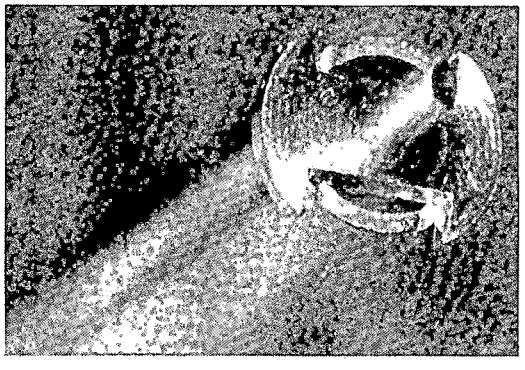


Fig. 2 (Blankenship and Aumayr). The inserter sleeve slots hold the infusion port wings for placement in the pars plana perforation.

REMOVAL OF BLOOD FROM THE RETINAL SURFACE IN PARS PLANA VITRECTOMY

MAURICE B. LANDERS III, M.D.
Durham, North Carolina

Removal of a thin layer of blood from the surface of the posterior retina is occasionally necessary during a pars plana vitrectomy. This thin film of blood is sometimes difficult to approach, particularly if the vitrectomy is being done with a side-opening instrument such as the Ocutome. S. Charles, M.D. (unpublished data), has proposed a retinal vacuuming technique for removing this layer of blood. In this procedure, a blunt-tipped 20-gauge needle is introduced through the opening in the pars plana previously prepared for the vitrectomy instrument and placed close to the surface of the film of blood lying on the retina, and its opening in the blunt-tipped needle is covered with the surgeon's finger. At the appropriate time, the surgeon lifts his finger from the opening, which simultaneously allows infusion fluid to flow into the eye and creates a suction effect at the tip of the needle. The thin layer of blood can then be vacuumed by the blunt-tipped needle. This excellent technique does have two drawbacks: (1) If the infusion fluid is maintained at an intraocular pressure of approximately 22 mm Hg, the rapid onset of the vacuum will cause a transorifice pressure of 22 mm Hg at the tip of the blunt 20-gauge needle. This vacuum may be sufficient in some cases to draw retina and other tissues into the blunt-tipped needle, which can result in a retinal tear or other retinal damage. (2) Upon opening the vacuum needle to the atmosphere, the intraocular pressure will drop to zero. Any tendency for the fragile blood vessels within the eye to bleed will be enhanced.

A minor modification in the vacuuming procedure eliminates these two drawbacks. The vacuum needle is not vented to the atmosphere, but is connected to a bag of physiologic salt solution such as lactated Ringer's solution, the same fluid which is used for the infusion (Figure). The height of the two bags of intravenous solution, and thus the column of water producing the intraocular pressure, is varied independently. If the fluid levels in both bags are equal, there will be no vacuum. If the bag connected to the vacuum needle is placed slightly lower than the bag attached to the infusion line, a small suction effect will be produced. Varying the height of the two bags allows the degree of suction to be precisely controlled and initiated slowly.

The problem of intraocular bleeding from fragile blood vessels can be minimized or even eliminated by elevating both bags of intravenous fluid to increase the intraocular pressure, which still allows the controlled retinal vacuuming to

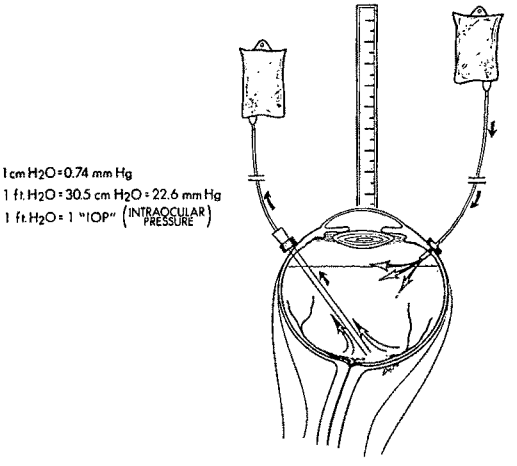


Figure (Landers). Suction pressure at the tip of the blunt needle near the retinal surface equals the difference in height of the fluid columns in the two bags of intravenous fluid.

From the Department of Ophthalmology, Duke University Eye Center, Durham, North Carolina.
Reprint requests to Maurice B. Landers III, M.D., Box 3802, Duke University Eye Center, Durham, NC 27710.

be carried out by placing the bag of intravenous fluid attached to the vacuum line slightly lower than the bag of intravenous fluid connected to the infusion line.

We have used this technique successfully on more than ten patients and have found it to be an effective method for removing blood from the retinal surface.

SUMMARY

The technique of removal of blood from the retinal surface in pars plana vitrectomy using a blunt-tipped needle open to the atmosphere has two disadvantages: uncontrolled suction force at the tip of the needle, and a drop in intraocular pressure to zero when the needle is vented to the atmosphere.

Modification of the procedure can eliminate these problems. By connecting the blunt-tipped needle to a bag of intravenous fluid, the suction force of the needle can be controlled; and by elevating both the bag connected to the infusion line and that connected to the suction needle, the intraocular pressure can be increased and the problem of intraocular bleeding minimized or eliminated.

LOCALIZER FOR RETINAL DETACHMENT SURGERY

ALLEN LANDERS, M.D.
New York, New York

A critical aspect of retinal detachment surgery using a modified technique of Custodis that consists of cryotherapy and scleral buckling with an exoplant, with or without drainage of subretinal fluid, is the accurate localization of the retinal tear. Diathermy application while observing with indirect ophthalmoscopy leaves a small burn visible on the surface of the sclera overlying the retinal tear being marked. Similarly, a cryoprobe can be applied while observing with indirect ophthalmoscopy, but this leaves no scleral mark. The surgeon must rotate the eye forward before the cryoapplication thaws and manually mark the scleral surface with a marking pen or cautery. A mechanical scleral marker such as the Uretts-Zavalia scleral pick, the Gass scleral marker,[1] or the O'Connor scleral depressor[2] may be used. After positioning these localizers while observing with indirect ophthalmoscopy, the surgeon applies pressure, causing a transient indentation mark on the scleral surface, which he then permanently marks with a marking pen or cautery. A disadvantage of this technique is the occasional difficulty in shifting the position of the mechanical localizer if it is engaged in superficial sclera, as well as the occasional presence of multiple indentation marks.

A new localizer (Fig. 1) that has two modes of action may overcome these drawbacks. In the undepressed state (Fig. 2, left), the Landers localizer has a smooth surface that will not engage or mark the sclera as the surgeon adjusts its position while observing with indirect ophthalmoscopy. When the optimum po-

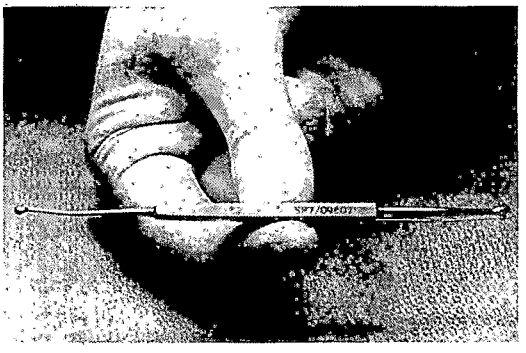


Fig. 1 (Landers). Landers localizer for retinal detachment surgery.

From the Retina Service, Manhattan Eye, Ear, and Throat Hospital, New York, New York.

Reprint requests to Allen Landers, M.D., 572 Park Ave., New York, NY 10021.

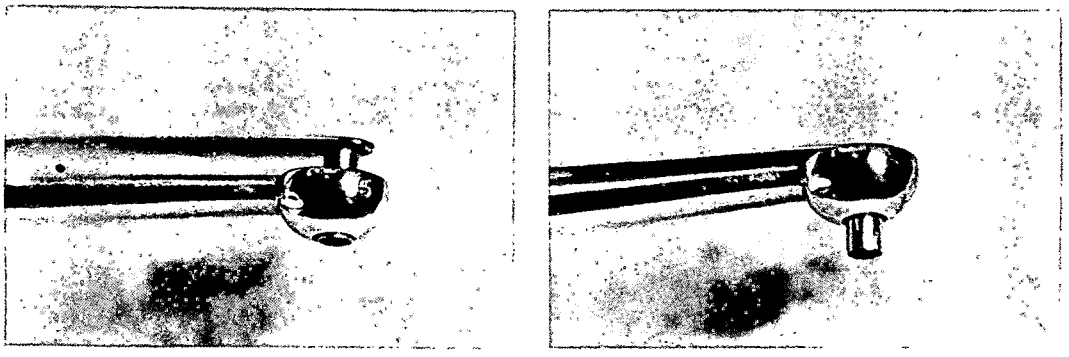


Fig. 2 (Landers). Left, Localizer in the undepressed state. Right, Localizer in the depressed state.

sition has been determined, the surgeon depresses the marking pick (Fig. 2, right), which engages the sclera in the center of the depressed area and leaves a transient indentation ring in the superficial sclera (Fig. 3). This spot is then permanently marked with a marking pen or a cautery. Additionally, the other end of this instrument is a simple rounded depressor for examining the peripheral retina.

SUMMARY

A new mechanical localizer for retinal detachment surgery has two modes of action. The localizer is positioned under visualization in the undepressed state to avoid engaging or marking sclera until the surgeon elects to depress the marking pick after optimum localization.



Fig. 3 (Landers). Transient scleral indentation mark.

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MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

AMERICAN OPHTHALMOLOGICAL SOCIETY—1978 MEETING

The American Ophthalmological Society, the oldest medical society in the United States, met again, May 29–31, 1978, in its most traditional haunt, the delightfully sprawling and nearly 100-year-old Homestead of Hot Springs, Virginia. The traditional three mornings of well chosen papers generated good discussions but without the more pyrotechnic exchanges of the Verhoeff and Bedell days. Yanoff, Mishkin, and Nichols recounted an unusual orbital sarcoid tumor that responded in two exacerbations to oral corticosteroids; the diagnosis was corroborated by conjunctival biopsy, which is positive in approximately 50% of orbital cases; computed axial tomography rendered high precision in mass measurement but less precision in terms of cytology. Kimura documented the occurrence of heterochromic cyclitis, both in brown-eyed patients and in darker irides. Though Fuchs' heterochromia accounts for only 3% of uveitis, a thorough appreciation of this etiology eliminates need for the protracted "uveitis work-up." Dr. Kimura cautioned against evoking hyphemia by anterior chamber tap in heterochromia because of frequently accompanying blood vessels in the angle. Robb, Ervin, and Sallan reported the histology in eyes obtained at autopsy following death from acute lymphocytic leukemia in 32 children and acute myelocytic leukemia in 22 children, ages 8 weeks to 19 years. Eight of the 60 patients had leukemic retinal infiltration. Such findings, coupled with high white blood cell counts, were routinely preterminal. Involvement of the choroid or less often, the optic nerve, was generally an associated finding with central nervous system infiltration. Sixteen eyes were normal.

Patz, Lutty, and Coughlin reported strikingly positive inhibition of retinal neovascularization by an extract of adult vitreous; conversely, neonatal vitreous, prepared in similar fashion, tends to stimulate new vessels. Fink, Cutler, and MacKay reported major problems of keratoconjunctivitis sicca with associated cholangiostatic hepatitis, pancreatic dysfunction, and xerostomia following antihelminthic treatment with thiabendazole. Anderson tabulated induced myopia with multiple exposures to therapy consisting of 85% to 95% O_2 at two atmospheres in treatment periods of two hours each over 40 sessions. Myopic shifts of 1 to 3 diopters persisted for three to four weeks and gradually returned to normal refraction after 15 weeks. There was no shift in keratometry findings.

In an extensive series of 116 patients undergoing surgical decompression of the orbit, Dyer reported better results than by muscle surgery alone, though surgery was subsequently necessary in most patients. Extraocular muscle surgery should be deferred until optimal recession occurs. Wolter, in another one of his classically precise histologic observations, reported on numerous efferent nerve fibers in the optic nerve stump of a 56-year-old patient who had died 16 days after enucleation. The Kupfers reported exuberant action of neural crest cells causing abnormalities either by migration or differentiation leading to abnormal chamber angle development and congenital glaucoma. Associated skeletal anomalies should be expected with aberration of the neural crest. O'Rourke presented a further overview of his continuing, meticulous animal studies of intraocular flow

by isotopic tracer yielding better understanding in the mechanisms of contusion injury and endophthalmitis as well as more physiologic variations.

Howard, Breg, Warburton, Miller, and McKeown, acknowledging that most retinoblastoma patients do not have chromosomal abnormalities, proceeded to demonstrate unilateral or bilateral tumors associated with partial deletion of the long arm of chromosome 13. Earlier studies lumping the D-group chromosomes together and without the assistance of banding underestimated the chromosomal role. Small segments of 13q were missing only in a few of the cells studied. It is necessary to examine many cells of various tissues and to use banding to understand the heredity of this neoplasm. Nearly 15% of children with 13q defects have retinoblastoma and may be retarded.

Burns, Conner, and Gipson reported on Schnyder's crystalline corneal dystrophy with its central ring-like deposits of cholesterol and marked circulus lipidis. These patients have active cholesterol uptake in the cornea; thus the dystrophy depends on abnormalities of blood lipid metabolism as well as autosomal dominant defects in keratocytes.

Harley, Rodriques, and Crawford reported histologic verification of the unusual congenital fibrosis syndrome involving one or all extraocular muscles. Family histories established an autosomal pattern. Hope, Potts, and Keeney analyzed 200 serially examined low-vision patients, revealing poor correlation between distance acuity and near aid need, preference for stand magnification with increasing age, best acceptance in early and mid life, and rejection for nonoptical reasons reaching 5% to 10% in late life. Kearns, Siekert, and Sundt reported superior ophthalmic and neurologic results with a new neurosurgical anastomosis of the superfical temporal artery to the middle cerebral artery instead of attacking the impaired ipsilateral common carotid; 121 patients undergoing this technique faired better than those with more traditional carotid surgery. Kennedy stressed arterial embolization for progressive hemangioma in infancy but used silicone spheres by catheter. Weinstein and Rylander, in an experimental study of macular photocoagulation in 12 monkeys and one human (in whom enucleation was to be performed for a peripheral melanoma), demonstrated remarkable correlation between histologic findings and visually evoked potentials.

Spaeth and Barber, one of the several teams simultaneously and independently discovering homocystinuria, ranged widely into the philosophic approach to genetically influenced diseases, stressing interrelationships of multiple gene defects and environmental overlay. Forbes presented a new limbal suspension to avoid collapse of the globe during intraocular surgery. A dramatic report by Troutman and Swinger analyzed their first 16 patients receiving keratophakia by the José Barraquer technique with a slight increase in complications. The intracorneal surgical site, exterior to the chambers of the eye, is however, an enormous safeguard in this physiologic approach.

The new president, Phinizy Calhoun, Jr., of Atlanta, follows a responsible pattern created by the retiring president, Sam McPherson, Jr. Six new associate members were introduced. The coveted Howe Medal was awarded to Rodman Irvine.

ARTHUR H. KEENEY

AMERICAN MEDICAL ASSOCIATION SECTION ON OPHTHALMOLOGY—1978

The Section on Ophthalmology of the American Medical Association met in conjunction with the AMA's 127th Annual Convention in St. Louis, June 20 and 21, 1978.

The chairman of the Section, Thomas D. Duane, called the meeting to order Tuesday, June 20, in the new St. Louis Convention Center. The opening paper, by Manus C. Kraff, Donald R. Sanders, and Howard L. Lieberman, was entitled "The effect of phacoemulsification on the corneal endothelium." Dr. Kraff, who read the paper, indicated that the loss of endothelial cell density is 34% in phacoemulsified eyes, as compared to a 17% loss in eyes undergoing intracapsular cataract extraction; the loss rate increases with ultrasound times greater than two minutes. In discussing this paper, Thomas O. Wood, stressed that the endothelium is "forgiving" in nature and that specular microscopy has permitted eye surgeons to be bolder than ever before.

Barry J. Wolstan, Robert C. Ramsay, David E. Eifrig, and William H. Knobloch, reported on "Visual prognosis following removal of intraocular foreign bodies." They noted a prognosis of approximately 50% for good visual acuity in their series, essentially changed from studies before the era of techniques such as microsurgery and pars plana vitrectomy. Glen P. Johnston noted that improved methods of diagnosis and therapy tend to be significantly more expensive than the traditional ones.

"Neuro-oculo-cutaneous hamartomatosis—A pedigree," was presented by Thomas R. Pheasant, Richard E. Goldberg, Jerry A. Shields, and Larry E. Magargal. Harold F. Falls, who discussed this presentation, suggested that these manifestations probably represent delayed development.

Thomas O. Wood reported on "Trifluorothymidine in resistant dendritic ulcers." He noted that corticosteroids did not retard healing of ulcers treated with this compound. In discussion, Stephen R. Waltman agreed that trifluorothymidine is an extremely effective agent.

Kenneth B. Mitchell, Theodore Krupin, Mark F. Johnson, and Bernard Becker reported on the "Long-term response following peripheral iridectomy in angle-closure glaucoma." They showed that peripheral iridectomies are safe and effective even over a long period of time. George L. Spaeth agreed that most, but not all, patients with acute, narrow-angle glaucoma required iridectomy.

Barry A. Maltzman discussed "Extended wear contact lenses," reporting that 84 of his 100 patients were able to wear lenses successfully. Oliver H. Dabezies, noted that new lenses for extended wear are to be released soon.

To open the afternoon session, Dr. Duane gave the Chairman's Address, entitled "The Section on Ophthalmology of the AMA. The phoenix phenomenon." Dr. Duane reviewed the history of the Section. Most of the great contributors to American ophthalmology have served the Section. However, the composition of the Section Councils was changed drastically by the AMA in 1977; as a result the continuation of the Section's activities was threatened. However, at a meeting June 19, 1978, the Section Council determined that the Section would continue to be a viable organization, which would conduct a scientific program. The program would either remain as part of the annual AMA meetings or would be held in conjunction with the American Academy of Ophthalmology.

Dr. Duane noted that the major problems facing ophthalmology today included the delivery of health care, research, and education. He stressed that ophthalmologists working together with the AMA could have a voice in all of these areas. He concluded by emphasizing that the AMA needs ophthalmology and that ophthalmology needs the AMA.

The scientific program continued with a presentation by M. Madison Slusher and William E. Hutton, "Vitreous instru-

mentation in anterior segment trauma and reconstruction." This surgical technique has permitted successful results in a wide variety of situations. In discussing this paper, Nicholas Douvas restated the objective of vitrectomy in trauma as the performing of definitive surgery as a one-stage technique.

Byron Smith and Richard L. Petrelli reported on "Dermis-fat graft for the correction of the exposed orbital implant." This method has the advantage of correcting cosmetically significant enopthalmos in anophthalmic patients. Charles R. Leone, Jr., discussed this paper, pointing out that previously held views concerning absorption necrosis and nonvascularization of fat grafts have been disproven by this work. He noted, however, that he still prefers the scleral patch graft for most cases.

B. Allen Watson discussed "Early surgery and congenital esotropia," demonstrating a computer-assisted linear analysis to develop his data. Of his 54 subjects, 29% achieved stereopsis. The paper was discussed by Marshall M. Parks, who emphasized that not all patients with congenital esotropia with peripheral fusion obtain stereopsis.

G. S. Guggino reported on "Six-millimeter bimedial recession in congenital large angle esotropia," indicating that this was reserved for patients with measurements of 60 prism diopters or greater. Of his 45 subjects, 43 were corrected with less than 10 prism diopters of esotropia, and there were no overcorrections. Eugene M. Helveston, who discussed this work, agreed with the recommendation for performing early surgery (5 to 12 months of age). He also pointed out that the insertion of the medial rectus muscle frequently varied from 3 to 6 mm in infants; the average was 4.4 mm.

"The surgical treatment of accommodative esotropia," presented by David Mittelman and Martin J. Urist, described good results in recessing one medial rectus muscle in patients who are not fully corrective with miotics or bifocals. Discussant James E. Miller agreed that there is an occasional need for surgery in these patients.

"The corneal endothelium and intraocular lens implantation. Specular microscopic studies," was described by Manus C. Kraff, Donald R. Sanders, and Howard L. Lieberman. Although they found only a small increase in endothelial cell loss compared to eyes undergoing intracapsular cataract extraction alone as long as the trauma to the endothelium was estimated to be mild, the rate of loss increased two- to threefold in patients who suffered moderate endothelial cell trauma. The discussant, Robert C. Drews, noted that some workers had found as much as a sixfold endothelial cell loss rate with "difficult" cases as opposed to "easy" cases.

On Wednesday, June 21, a postgraduate course, entitled "Ophthalmology for the non-ophthalmologist," was given by Thomas Behrendt, course director, Edward A. Jaeger, and J. Wallace McMeel, Jr. This course was well attended by family practitioners and others interested in ophthalmology.

The Section on Ophthalmology continued with a paper by Ramesh C. Tripathi and Frank W. Newell, "A clinicopathologic study of vitreous opacities in amyloidosis." They noted the presence of peculiar vitreous footplates attached to the posterior surface of the lens in their patients. The discussant, Thomas D. Duane, emphasized the importance of a conjunctival biopsy when this diagnosis is being considered.

"Venostasis retinopathy," was described by Charles R. Beyrer, who agreed with the original description of this entity distinguishing it from hemorrhagic retinopathy. Venostasis retinopathy, as described by Hayreh, is a benign self-

limiting disease that rarely leads to hemorrhagic retinopathy.

Barry E. Wright and Alan C. Bird presented material on "Placoid pigment epitheliopathy and Harada's disease," which they consider to be a clinical continuum. This paper, which received the Section's award and a prize of $250 for the best paper of the meeting, emphasized the fluorescein angiographic similarities of both conditions with nonfilling of the choriocapillaris leading to ischemic changes in the retinal pigment epithelium. In discussing this paper, Froncie A. Gutman noted a few obvious clinical differences between the two conditions, especially the self-limiting nature of placoid pigment epitheliopathy as opposed to the chronic recurrent aspect of Harada's disease.

Hernando Zegarra, James Conforto, Edward M. Chester, Robert T. Spector, and John Hines described clinical and hematologic correlations of "Leukemic retinopathy." They pointed out that there was no definite correlation between the clinical status of the patient and the appearance of the retinopathy. Walter R. Stafford, the discussant, stressed the common occurrence of ocular involvement in leukemia.

Robert A. Schimek described, "Ophthalmic manifestations of visceral larva migrans." He emphasized that the ELISA test is the most reliable study for the diagnosis of this disorder. Ramesh C. Tripathi discussed the differences between the ocular manifestations of toxocariasis and visceral larva migrans, stressing that they were rare in the latter instance.

Donald R. May, Gholam A. Peymen, Motilal Raichand, and Michael L. Klein reported on "Randomized prospective study of xenon arc panretinal photocoagulation for central retinal vein occlusion." The discussant, Stuart Fine, emphasized the large areas of nonprofusion of retinal capillaries as the basis of the neovascular glaucoma.

W. Rex Hawkins described "Macular pucker following retinal detachment surgery." Careful fundus examination showed open retinal holes in eight of his 26 patients. Seven of these had scleral buckles and underwent revision of their scleral buckles; all improved. In discussing this paper, Edward Okun agreed that unclosed breaks may explain some cases of macular pucker because of residual fluid permitting preretinal and subretinal cellular migration. He stressed the importance of closure of all retinal breaks in this as in other cases of retinal detachments.

Stuart L. Fine reported on "Randomized clinical trials for branch vein, senile macular degeneration, and presumed ocular histoplasmosis syndrome." He announced that five centers are currently studying these conditions and are presently enrolling patients in order to determine the therapeutic effectiveness of photocoagulation.

The Scientific Program concluded with a splendid symposium, "Glaucoma filtering surgery," moderated by Bernard Becker. The Distinguished Foreign Guest, Peter Gordon Watson of Cambridge, England, was introduced by Dr. Duane. Mr. Watson's presentation, "Trabeculectomy and the pathophysiology of glaucoma," was the first Parker Heath Memorial Lecture. He presented the results of trabeculectomy on 416 patients with various forms of glaucoma. The success rate of controlling increased intraocular pressure was high and complications were extremely low. His pathologic studies in these cases revealed extracellular accumulation of material clogging up the trabecular meshwork with loss of the normal vacuolar system. Trabeculectomy apparently permits the autoregulatory mechanism of the eye to be restored, leading to the conclusion that trabeculec-

tomy is an effective form of treatment for patients with chronic primary glaucoma. Mr. Watson ended by recommending that "the patient with chronic, open-angle glaucoma not easily controlled with pilocarpine 2% given three times daily should have trabeculectomy because it is a safe and predictable procedure."

The symposium continued with a report, "Use of setons in filtering surgery," by Theodore Krupin. Dr. Krupin indicated that use of a pressure sensitive glaucoma valve implant had controlled intraocular pressure in 16 of 25 patients. All these patients previously had surgical failures. Of 24 patients with neovascular glaucoma, 17 had intraocular pressure controlled as well by this technique. Harold G. Scheie presented his data, "Iridectomy with scleral cautery. Its use over a period of 25 years." The success rate of 25% was achieved in patients with chronic glaucoma. Dr. Scheie now uses a scleral flap with a highly beveled incision, closing this with a single 10-0 nylon suture under the conjunctival flap. George L. Spaeth presented "Combined cataract and glaucoma surgery," stating that those at greatest risk with glaucoma and cataract were those with pathologic cupping of the disk. The transient increase in intraocular pressure in the early postoperative period may produce significant visual field loss in these patients.

The session closed on a note of hopefulness despite the recent reorganization of the Section on Ophthalmology. The present officers are: Thomas D. Duane, chairman; Theodore Steinberg, vice chairman; and Oliver Dabezies, secretary.

GEORGE W. WEINSTEIN

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FRANK W. NEWELL, M.D.
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AMERICAN JOURNAL OF OPHTHALMOLOGY

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A VISIT TO THE PEOPLE'S REPUBLIC OF CHINA

There is always a tendency to pontificate about one's observations after a brief visit to a country where the customs differ markedly from those at home. I am sure the readers of THE JOURNAL are wise enough to keep this in mind in evaluating the comments in this editorial.

I had always thought of China as a country made up of industrious, intelligent people who reached a high culture level early in known history. It was one of the most heavily populated geographic areas with a high birth rate. The country was divided into a number of provinces, separated from one another by customs, language, and governmental control. The distribution of goods and wealth was markedly skewed. Periodically millions of people died from famine, as a result of draughts and floods.

In 1949, Mao Tsetung and the Communist party gained control of the country. Chairman Mao rapidly became not only the administrative but also the moral leader of the country. All land and wealth were taken over by the State. We were told that under this system production of food increased, but periodic shortages still existed. In order to gain better governmental control and to increase food productivity, the commune system was instigated in 1956. These communities varied markedly in size from areas of a few square miles to 100 square miles, with a population of a few thousand to as many as 80,000 to 100,000 people. From 1949 through 1972 the country was closed to visitors with but a few exceptions. Thus, our knowledge of the restrictions of freedom placed on the citizens was fragmentary. There were reports of marked hardship for the nonconformist, especially during the cultural revolution that began in 1966 and reached its peak in the last years of Mao when the government came under the control of the Gang of Four.

After President Nixon's visit to China

in 1972, selected individuals from the United States were allowed to visit the country. Dr. Harold Spalter of New York attempted to arrange a tour of the country for a group of ten ophthalmologists, but visas were refused. In 1977, China was opened to tourism and approximately 50,000 visitors were admitted. In 1978, an estimated 100,000 will be accommodated, approximately 5,000 from the United States.

In the fall of 1977, Dr. John Holmes of Honolulu arranged through the Asia Pacific Ophthalmological Society for a group of ophthalmologists and their wives to visit China after the International Congress of Ophthalmology in Kyoto, Japan. Dr. Holmes wrote many letters to the ophthalmological societies and to ophthalmologists in China, but received no answers. Dr. Arthur Lim of Singapore and Dr. Gerald Crock of Australia, both of whom had visited mainland China on separate occasions, told us there were strict protocols that we should follow in order to obtain the most productive exchange with our ophthalmic colleagues, and to enjoy the greatest insight into the ways of life of the people of China. Depending on our adherence to these guidelines, we would be graded as friendly, neutral, or unfriendly and our exchange would be regulated accordingly. Our group consisted of 28 persons, all of whom were delightful companions and excellent travelers. We must have been graded as friendly, for we were shown almost everything we requested and were given complete freedom within the cities to go where or do what we desired.

Our guides, Mr. Chang and Mr. Wu from the Luxingshe Travel Agency, a branch of the State Department, were excellent ambassadors of goodwill.

Some of the things that impressed me most about the people and the country were as follows:

1. There are no fat or starving Chinese. People seemed healthy and athletic. Transportation is either by foot or bicycle. All automobiles are State-owned.

2. The people are very industrious. There is no unemployment. They work six days a week, have no vacations, but do have scattered holidays that amount to some ten to 12 days per year.

3. Their system is semicapitalistic in that a factory worker or a worker in a commune may earn 300 to 500 yuan a year (1.7 yuan = $1.00). These earnings are based on a point system in which the worker is graded periodically on his skill and productivity. An unskilled or lazy worker makes less than a skilled more productive one. An executive, a mayor or leader, or a professor, depending on his ability, may earn as much as 800 to 1,000 yuan per month. All persons are encouraged to save, and 3.7% interest is paid on their accounts. Mr. Chang pointed out that this interest rate was better than that in the United States because inflation in China was almost zero.

4. The intensity of farming is almost beyond belief. In our travels around and between Peking, Shanghai, and Canton by bus and by train, every foot of land for hundreds of miles was under cultivation, even small strips of 100 square feet or less were planted with rice. Each blade had been sowed in a preparatory area and at a later date transplanted entirely by hand to the fields.

The commune we visited covered an area of approximately 42 square miles; the inhabitants were proud of their 400 tractors. These machines were three-wheel carts that consisted of an open motor with a belt drive to the front wheel. These were used more for hauling goods than for cultivation of the fields. We were told that the commune system had been efficient in increasing food productivity. Through this system the local communities had built reservoirs and irrigation canals, which had prevented major crop

disasters. The commune we visited had had to buy grain initially from the State, but in recent years production had increased to where they were able to sell 25% of their harvest to the State. Another evidence of financial incentive was in the tax structure. The central government imposed a basic 12% tax on the gross harvest, but if the output exceeded the quota, the tax was reduced progressively to 4%.

5. Chairman Mao was able to centralize the Chinese governmental control for the first time in history. He developed an orderly chain of command from the central government, to the province, to the brigade, to the team, to the family, and to the individual. We heard many complaints of restrictions of liberty in past years imposed by the Gang of Four, but none of these were directed against Chairman Mao. The literacy rate in China before 1948 was reported to be approximately 10%. At the present time it is said to be 90% among the younger generation. All children are taught Mandarin and a foreign language such as English, German, or French. These languages are in addition to their native dialects, which like Chinese and Cantonese, are so totally different from Mandarin that a translator is needed for interpretation. The control of the people is accomplished through constant propoganda, which is found in children's books, the theatre, concerts, public address systems in the factories, and posters on the streets. Group discussions are frequent in all units, and constructive criticism is a constant theme.

6. Chairman Mao was and is the spiritual leader of the country. In his writings he borrowed many concepts from the great religions. Thus, each person is encouraged to help his neighbor and if, for example, a child is doing poorly in school the better students assist him after hours so that he may keep up with the group. Major crime and petty theft are almost nonexistent. Hotel rooms are kept unlocked, and valuables do not disappear. We walked the waterfront in the shipping areas at night and were not bothered or molested. Mao's sayings and philosophies have practically replaced religion among the younger generation, although some of the older people still worship at their temples and churches.

7. The population explosion is under control. The growth rate now stands at 0 for the between 800 and 900 million people in China. They claim this was accomplished because Chairman Mao told them that their country was overpopulated and that they could not advance into an industrial nation without decreasing their growth rate. Most couples, in the cities at least, now have only one or two children.

8. Society in China is unquestionably regimented, but the people with whom we talked, both on the streets and in the shops, accepted this way of life because of the improved conditions that it has brought. They appeared to be happy and were very friendly to us. In Peking, Shanghai, and Canton we spent at least a day in hospitals with our ophthalmic colleagues. They are extremely capable and are conversant in ophthalmic literature, especially through THE JOURNAL, the Archives of Ophthalmology, and other publications from the United States. The distinguished colleagues in our group were immediately recognized and their works referred to in specific instances. The Chinese diagnostic ability appeared to be excellent; their knowledge of therapeutics was good; and most drugs for the treatment of eye infections were available to them. They practiced a combination of what they considered the best of Western and Chinese medicine. The Chinese medicine that we viewed was acupuncture, herbal medicines, and eye exercises for myopia. We were told that myopia was relatively common among the Chinese, although few people on the street wore

glasses. Likewise, in the factories where cloisonne, lacquered vases, and carved jade were made, neither microscopes nor glasses were used in performing this exacting and meticulous work.

The principle eye diseases in the hospitals and clinics consisted of trauma and infection. Consequently, retinal detachments and corneal transplants were among the most common surgical procedures. These operations were done without the aid of magnification. Surgical instruments were limited. The dexterity of the surgeons was excellent. One of the most notable deficiencies in equipment was the absence of binocular indirect ophthalmoscopes. This was especially true because of the large number of retinal detachments.

We were told that acupuncture was used in only about 20 to 30% of ophthalmic operations, primarily in stoic individuals and only at request of the patient. During an iridencleisis that we observed where acupuncture was used, topical anesthetics were also applied and the acupuncture acted primarily as akinesia of the eyelids.

We had a productive visit with Dr. Chang in the Workers, Peasants, and Soldiers Hospital in Peking. He was one of the co-isolators of the trachoma agent, and a most intelligent and pleasant person.[1] We also met Dr. Eugene Cheng, who in the late 1930s had been a member of the Wilmer Institute in Baltimore. He established the leading eye hospital in Canton. During the cultural revolution, he was placed under house arrest because he was accused of trying to promote himself above others in developing an outstanding eye hospital.

Our Chinese colleagues were anxious to establish communication and exchange ideas with ophthalmologists from other lands. I believe we have much to learn from them, particularly from their delivery of health care services.

Medical care is definitely structured and begins with education of the family. Dr. Chang told us it is through this mechanism that fresh cases of trachoma have almost been eliminated in China. The next steps up the ladder are the barefoot doctor or worker doctor, the commune clinic, the commune hospital, the municipal hospital, regional hospital, specialty and university hospital. At the eye hospital in Canton, Dr. Tu explained to us how medical teams from their hospital went to the countryside to educate the people about eye care, and to train barefoot doctors, commune physicians, and province doctors. They consider this form of prophylactic eye care equally as important as the surgical care given in their hospital.

I believe I can speak for my colleagues on this trip to mainland China in stating that this was one of the most interesting experiences we have ever had. China now produces sufficient food such that they are looking forward to industrialization. Their new constitution under Chairman Hua has decreed that China should be an industrialized nation by the year 2000. Our Chinese ophthalmic colleagues are excellent physicians, although their instrumentation and laboratory research are currently limited. We look forward to further collaboration with them and especially to their visits to our national and international meetings in this country. As President of the International Congress of Ophthalmology for 1982, I hereby extend to them an official invitation to meet with us in San Francisco, or to attend any of our conferences. As is their custom, I would like to ask them for their constructive criticism of this editorial.

A. EDWARD MAUMENEE

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OBITUARY

John Charamis, M.D.

John Charamis, who died Jan. 14, 1978, was the epitomé of an international ophthalmologist—charming, affable, and witty, he spoke five languages with ease. His ophthalmic instruction came from the leading world figures of ophthalmology: Baillart, Magitot, and Terrien of Paris; Kruckmann of Berlin; Van der Hoeve of Utrecht, and Clausen of Hälle.

Using the knowledge he acquired from ophthalmological societies in other countries, he founded the Greek Ophthalmological Society in 1931. He had an unequalled record for participating in the meetings of the International Congress of Ophthalmology, including The Hague in 1929, Madrid in 1933, and Cairo in 1937. Often referred to as "The Duke-Elder of Eastern Europe," he was a major figure with Sir Stewart in reviving the Congress after World War II in London in 1950, and he presented papers and films at all of the meetings every four years since that time. From 1966 to 1970, he was the President of the International Council of Ophthalmology and President at the Mexico meeting in 1970. He had made plans to participate in the Kyoto meeting in 1978.



John Charamis, M.D.

From 1933 to 1967, he directed the Eye Department of the Greek Red Cross Hospital and during World War II the Eye Center of the Seventh Military Hospital of Greece. He became Professor of Ophthalmology of the University of Athens, and from 1947 until his death he directed the Ophthalmiatrion. (the Eye Clinic founded by Queen Amalia of Greece in 1834). During 1958 and 1959 he was the dean of the Faculty of Medicine of the University of Athens. He became the president of the Greek Ophthalmological Society in 1950, and later was elected honorary life president.

In the service of his country, he was an Honorary Physician of the Greek royal family from 1948 to 1964, and in 1961, was the Minister of Health and Welfare for Greece and served as an advisor for the World Health Organization.

Dr. Charamis was one of the main organizers of the European Ophthalmological Society, and served as president of the First Congress of the Society held in Athens in 1960. He remained as one of its chief enthusiasts and advisors. In recognition for his outstanding efforts, the European Ophthalmological Society established the "Charamis Medal," to be awarded to a European ophthalmologist whose surgical contributions aid in the expansion of European ophthalmology. Dr. Charamis was an active or an honorary member of over 20 ophthalmic associations in Europe, North, Central, and South America. He served as the editor or associate editor of nine leading ophthalmic journals. Between 1927 and 1977, he published more than 370 original papers

in Greek, French, English, German, and Italian. He wrote the Greek textbook on eye surgery, a major contribution. He was one of the first to operate successfully for cataract and glaucoma simultaneously.

A listing of the honors he received would occupy an entire column, but outstanding among the many are the Commander of the Order of George First and Phoenix and the Gold Cross of the Hellenic Red Cross. From France, he received the Commander of the Legion of Honor; from Belgium, the Commander of the Crown; from Italy, Commander of the Merit of Italy; from Spain, Commander of the Merit; the Gold Medal of Mexico; and the Gold Medal of the League Against Trachoma. The Helmholtz Medal was awarded to him in Hamburg in 1976, and in his native Greece, he received the Trentas Medal.

Dr. Charamis is survived by his wife, Angela their son, Spilias, and their daughter, Lily Veniselas.

ALSTON CALLAHAN

CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper, with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

International Glaucoma Society

Editor:

We wish to inform the readers of THE AMERICAN JOURNAL OF OPHTHALMOLOGY that the International Glaucoma Committee has established an International Glaucoma Society to provide an international setting for the exchange of new trends on the subject of glaucoma.

The society will hold an International Glaucoma Symposium at the time of every International Ophthalmology Congress. The next symposium will be held in San Francisco in 1982.

Those interested in joining the International Glaucoma Society should write to John Hetherington, Jr., M.D., Room 775, N.C.B. University of California Medical Center, San Francisco, CA 94102.

W. LEYDHECKER, M.D.
President, International Glaucoma Committee
J. FRANÇOIS, M.D.
President, International Council of Ophthalmology
J. HETHERINGTON, JR., M.D.
Local Organizing Secretary
S. M. DRANCE, M.D.
Local Organizing Secretary

Effect of Corneal Section On Early Increased Intraocular Pressure After Cataract Extraction

Editor:

In the article, "The effect of corneal section on early increased intraocular pressure after cataract extraction" (Am. J. Ophthalmol. 85:337, 1978), by L. Rothkoff, B. Biedner, and M. Blumenthal, the authors proposed that increased intraocular pressure after cataract extraction is probably the result of trabecular damage caused by the incision. Lack of a rise in intraocular pressure in cataract extractions with a corneal section (incision) in a control group seems to support this view.

I believe that a more likely explanation for the rise in intraocular pressure after cataract extraction with a corneoscleral incision is destruction of episcleral veins in the area where the conjunctival flap was raised.

A corneoscleral section usually does not damage the trabecular network or Schlemm's canal because the inner opening of the wound is more centrally located

in a stepwise incision, which is further away from the chamber angle than the outer incision.

K. D. TEICHMANN, M.D.
Edmonton, Alberta, Canada

Genetic Etiology of Retinoblastoma

Editor:

The etiology of retinoblastoma can often be demonstrated to be genetic, sometimes on a Mendelian mutation basis and sometimes on a cytogenetic basis. In the latter instances, a characteristic, though not exclusive, mechanism involves deletion of at least a portion of a small segment of chromosome 13's long arm, specifically band 13q14 or a portion thereof.[1] Addressing the association of chromosome 13 deletions [del(13q)] and retinoblastoma, H. E. Cross, R. C. Hansen, G. Marrow III, and J. R. Davis published a provocative study, "Retinoblastoma in a patient with a 13qXp translocation (Am. J. Ophthalmol. 84:548, 1977). However, I believe their rendering of their data was incomplete, and because of its general importance, the material warrants closer scrutiny.

I believe Cross and associates failed to recognize that their patient was a mosaic as evidenced by comparing the der(X) chromosomes from their Figures 2 and 3. One cell line, exemplified by their Figure 2, shows the der(X) to include 13q intact from band q12 to 13qter. The second cell line, depicted by the partial karyotype of their Figure 3, shows the translocated 13q segment to have been partially deleted, apparently with loss of all of band 13q21 and approximately the distal half to two thirds of band 13q14, as judged from the chromosomal photographs and densitometry tracings. Moreover, with the 13q12 breakpoint appropriate for Figure 2, and judging from the appearance of the q terminus of the der(13) it would seem that the pterX has been translocated to the der(13). Thus, the karyotype signature for their patient (as a whole) should be as follows: 46,X,−X,−13,+der(X)(13qter → 13q12::Xp22 → Xqter),+der(13)(13pter → 13q12::Xp22 → Xpter)/46,X,−X,−13, +der(X)(13qter → 13q22::13q14 → 13 q12::Xp22 → Xqter),+der(13)(13pter → 13q12::Xp12 → Xpter). The major point of the authors apparently overlooked that a secondary interstitial deletion had occurred after the primary reciprocal translocation event, establishing mosaicism for two abnormal cell lines, including one with a de novo deletion involving the 13q14 band of the der(X). Their surmise that a segment of 13q14 was lost is substantiated by their own data. This is an important point; otherwise, their interpretations were at odds with the association of 13q deletions and retinoblastoma uniformly involving band 13q14.

VINCENT M. RICCARDI, M.D.
Houston, Texas

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Keratoconus in Contact Lens Wear

Editor:

In their provocative article, "Hard contact lens wear as an environmental risk in keratoconus" (Am. J. Ophthalmol. 85: 339, 1978), A. R. Gasset, W. L. Houde, and M. Garcia-Bengochea failed to establish the association claimed. They have confused prospective and retrospective analyses and overlooked an area of potential bias.

One of 1,248 patients in their soft contact lens clinic eventually developed keratoconus. In epidemiologic parlance this is a prospective analysis, beginning with a known population (soft contact lens wearers) followed over time for the

onset of a clinical condition (keratoconus). The authors contrast these findings with their observation that 27% of known keratoconus patients had a prior history of hard contact lens wear. This is a retrospective anlaysis, since it begins instead with patients already having the clinical end point (keratoconus), and determines the proportion with the potential risk factor (hard contact lens wear). Retrospective and prospective analyses obviously measure entirely different things and mixing the two is like comparing "apples and pears."

There is also a problem with the authors' choice of controls. They assure us the refractive error of the two groups was comparable. Although this may have been true for their spherical equivalents, it seems unlikely that the proportion of cases with irregular or high degrees of astigmatism was similar, since these conditions require the choice of hard contact lenses. Presumably early in keratoconus, before the diagnosis is clear, a significant proportion of cases will suffer irregular or high degrees of astigmatism. A population of hard contact lens wearers will therefore automatically contain a larger proportion of future keratoconus patients than a population of soft lens users.

ALFRED SOMMER, M.D.
Bandung, Indonesia

Reply

Editor:

In his letter, Dr. Sommer deals with two factors: (1) the type of epidemiology study he thinks our study is, and (2) what he thinks keratoconus is.

The special or particular contribution of epidemiology lies in the study of the determinants of disease. This involves an interpretation of the distribution of disease in terms of possible causal factors. The use of epidemiologic methods in this manner to identify causal association is sometimes called analytic epidemiology. There are three main groups of epidemiologic studies: (1) descriptive studies, (2) analytic studies, and (3) experimental studies. Analytic studies specifically designed to examine a particular hypothesis, that is, the role of hard contact lens wear in the development of keratoconus, were more suitable for our study. The analytic studies can also be divided into two main groups, the case history study and the cohort study. We used the case history investigation in our study for the following reasons: (1) One begins with a fixed number of cases and there needs to be relatively little concern for low incidence of the disease. For example, if one considers an average incidence of keratoconus of 1 in 10,000, we would have had to study 1,620,000 cases to obtain a sample of the same size as the one we used in our paper. (2) Age of onset: It is generally accepted that the average age of onset of keratoconus is 18 years. Therefore, if our consultand, that is, if the person whose genotype we are evaluating is still unaffected at 20, 25, or 30 years old, the greater the probability that he did not inherit the biologic genetic factor presumably necessary for the development of keratoconus.

Dr. Sommer's dogmatism could be caused by his confusion about keratoconus. Although it is relatively easy to find a cause in an iatrogenic disease with a simple unitary etiology, keratoconus results from the interplay between multiple biological (genetic) and environmental factors. Even when the environmental contribution is considered apart from the inheritance as it was in our paper, multiple interaction between host factors and environmental factors can be expected to be responsible for the development of events leading to the inception and progression of the disease. Dr. Sommer's difficulties in diagnosing keratoconus are his own. Before the diag-

nosis of keratoconus can be made, it has to be suspected. The progress of myopia in keratoconus is not axial but curvature myopia, which can be objectively evaluated with the keratometer.

We conducted our study by using the analytic investigation, case history study. However, the lack of a better control group prevented us from even attempting to use statistics to prove our hypothesis. Therefore, a causal relationship was never proposed; instead, we formulated a hypothesis of circumstantial association between hard contact lens wear and the development of keratoconus. A review of the published reports shows that similar epidemiologic studies have made enormous contributions to medicine: aniline dye and carcinoma of the bladder, asbestos and lung cancer, fluoridation and dental cavities, oxygen and retrolental fibroplasia, to name a few examples. Finally, as Sir William Osler said: "The greater the ignorance, the greater the dogmatism."

ANTONIO R. GASSET, M.D.
Gainesville, Florida

BOOK REVIEWS

Neuro-ophthalmology. By Joel S. Glaser. Hagerstown, Maryland, Harper and Row, Inc., 1978. Hardcover, 364 pages, table of contents, index, 220 black and white figures, 3 color plates. $35

This textbook was published previously as a section in "Clinical Ophthalmology," the superb five-volume loose-leaf series edited by Thomas D. Duane. In revising the original section from "Clinical Ophthalmology," a separate index was added and each chapter now begins with a short outline.

Joel Glaser wrote the first eight of the 15 chapters of the text. In Chapters 1 to 3, he discusses neuro-ophthalmologic history and physical examination. In Chapter 4, he studies the anatomy of the visual sensory system. In Chapters 5 through 7, Glaser discusses the prechiasmal, chiasmal, and retrochiasmal visual pathways, respectively. In Chapter 8, he reviews the pupil and accommodation. Robert Daroff, Louis Dell'Osso, and Todd Troost were responsible for Chapters 9 to 11, which comprise a section on the ocular motor system. These chapters contain many bioengineering terms and the authors have provided a separate glossary for this section. In Chapters 9 to 11, the authors discuss eye movement characteristics and recording systems, supranuclear disorders of eye movements, and nystagmus and related ocular oscillations. Joel Glaser wrote Chapters 12 and 13 concerning infranuclear disorders of eye movements and congenital anomalies of innervation. Todd Troost discusses migraines and related conditions. Glaser and Troost are co-authors of Chapter 15, which reviews aneurysms, arteriovenous communications, and related vascular malformation.

The text provides a concise survey of neuro-ophthalmologic topics. The references at the end of each chapter are extensive and up-to-date. The index is 12 pages long and is well organized. The photographs are generally of high quality. One disappointing feature of the text is the cursory discussion of computed tomography. This noninvasive radiologic technique has become an important diagnostic tool and could have been more fully covered. No illustrations of computed tomography scans appear in the text.

Although this book is not as comprehensive as "Clinical Neuro-ophthalmology" by Walsh and Hoyt, it is current, concise, well written, and can be highly recommended to the resident in training as well as the practicing ophthalmologist.

WALTER JAY

Controversy in Ophthalmology. Edited by Robert J. Brockhurst, S. Arthur Borvchoff, B. Thomas Hutchinson, and Simmons Lessell. Philadelphia, W. B. Saunders Company, 1977. Clothbound, 959 pages, table of contents, index, 93 tables, 205 black and white figures, 1 color plate. $42.50

This is an exceptionally interesting book that provides support for a variety of different ophthalmic opinions. The text is arranged in a series of discussions that lead off with an introductary statement by one or two of the editors, followed by the views of an advocate of a particular opinion and then a further discussion by another expert that is not necessarily directly opposed to the earlier view, but not in total agreement. The editors then provide a concluding comment. They selected some of the leading ophthalmologists in the United States and Britain to debate their concepts about a variety of themes.

The some 30 topics included cover a diversity of material that ophthalmologists often discuss: phacoemulsification, absorbable and nonabsorbable sutures, cataract surgery, management of subluxated lenses, postoperative care of the cataract patient, prone or upright gonioscopy, ocular hypertension or early glaucoma, trabeculectomy, and other filtering operations, flat anterior chamber after filtering, intraocular lenses, glaucomatous atrophy, diagnosis of orbital lesions, surgery or radiation for eyelid cancer, surgery of blowout fractures, time of surgery for congenital strabismus, corticosteroids in herpes simplex infection, vitreous surgery, retinal holes without detachment, management of slowly progressive malignant melanomas, diabetic retinopathy, serous choroidopathy, histoplasmosis, uveitis treatment and diagnosis, developmental dyslexia, optic neuritis treatment, and gliomas of the anterior pathway.

Many of these are topics about which there is discussion and sometimes strong feelings, which are often the result of insufficient observation or a limited opportunity for study. The views of the authors are always provocative. The editors have selected many of the chief proponents of a particular viewpoint and their introduction and subsequent comments do much to place the discussions in context. The volume is highly recommended for those practitioners who seek a balanced presentation of differing viewpoints.

FRANK W. NEWELL

SYMPOSIA

Advances in Ophthalmology, Volume 35. Edited by M. J. Roper-Hall, H. Sautter, and E. B. Streiff. Basel, Switzerland, S. Karger AG Medical and Scientific Publishers, 1978. Clothbound, index, 58 black and white figures, 9 tables. $72

FRANÇOIS, JULES: **Heredity of the choroidal dystrophies**

HAASE, WOLFGANG: **Optische penalisation als therapeutisches hilfmittel beim fruhkindlichen strabismus**

JERNDAL, TORD, AND SVEDBERGH, BJÖRN: **Goniodysgenesis in exfoliation glaucoma**

TSUKAHARA, SHIEGEO: **Hyperpermeable disc capillaries in glaucoma**

TSUKAHARA, S., NAGATAKI, S., SUGAYA, M., YOSHIDA, S., AND KOMURO, Y.: **Visual field defects, cup-disc ratio and fluorescein angiography in glaucomatous optic atrophy**

LEUENBERGER, P. M.: **Morphologie fonctionnelle de la cornée**

DEMELER, U.: **Verlaufskontrollen von iristumoren mit hilfe der fluoreszenzangiographie**

The Ocular and Cerebrospinal Fluids. By L. Z. Bito, H. Davson, and J. D. Fenstermacher. London, Academic Press, 1977. Hardcover, 561 pages, table of contents, over 300 black and white figures, 1 color plate. $39

BRIGHTMAN, M. W.: Morphology of blood-brain interfaces

RAVIOLA, G.: The structural basis of the blood-ocular barriers

TRIPATHI, R. C.: The functional morphology of the outflow systems of ocular and cerebrospinal fluids

GOMEZ, D. G., AND POTTS, D. G.: Effects of pressure on the arachnoid villus

SEGAL, M. D., AND POLLAY, M.: The secretion of cerebrospinal fluid

WRIGHT, E. M., WIEDNER, G., AND RUMRICH, G.: Fluid secretion by the frog choroid plexus

MAREN, T. H.: Ion secretion into cerebrospinal fluid

COLE, D. F.: Secretion of the aqueous humour

OLDENDORF, W. H.: The blood-brain barrier

LEVIN, E.: Are the terms blood-brain barrier and brain capillary permeability synonymous?

KAUFMAN, J. J., KOSKI, W. S., AND BENSON, D. W.: Temperature and pH sensitivity of the partition coefficient as related to the blood-brain barrier to drugs

LORENZO, A. V.: Factors governing the composition of the cerebrospinal fluid

BITO, L. Z., AND WALLENSTEIN, M. C.: Transport of prostaglandins across the blood-brain and blood-aqueous barriers and the physiological significance of these absorptive transport processes

MAREN, T. H.: Ion secretion into the posterior aqueous humor of dogs and monkeys

BRADBURY, M. W. B., AND SARNA, G. S.: Homeostasis of the ionic composition of the cerebrospinal fluid

ABBOT, N. J., PICHON, Y., AND LANE, N. J.: Primitive forms of potassium homeostasis. Observations on crustacean central nervous system with implications for vertebrate brain

BITO, L. Z.: The physiology and pathophysiology of intraocular fluids

BILL, A.: Basic physiology of the drainage of aqueous humor

TRIPATHI, R. C.: Uveoscleral drainage of aqueous humour

BILL, A.: A reply to R. Tripathi: Uveoscleral drainage of aqueous humour

LANGHAM, M. E.: The aqueous outflow system and its response to autonomic receptor agonists

DOMER, F. R.: Basic physiology of cerebrospinal fluid outflow

MCCOMB, J. G., DAVSON, H., AND HOLLINGSWORTH, J. R.: Attempted separation of blood-brain and blood-cerebrospinal fluid barriers in the rabbit

WELCH, K.: Selected topics relating to hydrocephalus

POTTS, D. G., AND GOMEZ, D. G.: Radiological studies of cerebrospinal fluid and hydrocephalus

SORENSEN, S. C., AND GJERRIS, F.: Adaptation of intraventricular pressure to acute changes in brain volume

HAKIM, S.: Considerations on the physics of hydrocephalus and its treatment

KUPFER, C., AND BALLINTINE, E. J.: The glaucomas

TRIPATHI, R. C.: Pathologic anatomy of the outflow pathway of aqueous humour in chronic simple glaucoma

LANGHAM, M. E.: The variability of the resistance to aqueous flow through the intrascleral venous plexus

KAUFMAN, P. L., BILL, A., AND BÁRÁNY, E. H.: Effect of cytochalasin B on conventional drainage of aqueous humor in the cynomolgus monkey

KAUFMAN, P. L., AND BÁRÁNY, E. H.: Recent observations concerning the effects of cholinergic drugs on outflow facility in monkeys

COGAN, D. G., AND KUWABARA, T.: Papilledema

JAMES, A. E., JR., FLOR, W. J., NOVAK, G. R., STRECKER, E.-P., BURNS, B., AND EPSTEIN, M.: Experimental hydrocephalus

CSERR, H. F., COOPER, D. N., AND MILHORAT, T. H.: Flow of cerebral interstitial fluid as indicated by the removal of extracellular markers from rat caudate nucleus

STERN, J., HOCHWALD, G. M., WALD, A., AND GANDHI, M.: Visualization of brain interstitial fluid movement during osmotic disequilibrium

EAKINS, K. E.: Prostaglandin and non-prostaglandin mediated breakdown of the blood-aqueous barrier

RAPOPORT, S. I.: Osmotic opening of blood-brain and blood-ocular barriers

YUDILEVICH, D. L., AND BARRY, D. I.: Indicator diffusion and other non-destructive methods for the study of experimental modifications of the blood-brain barrier

SAUNDERS, N. R.: Ontogeny of the blood-brain barrier

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

Annals of Neurology

PAPILLOPHLEBITIS: BENIGN RETINOPATHY RESEMBLING PAPILLEDEMA OR PAPILLITIS. Ellenberger, C., Jr., and Messner, K. H. (Milton Hershey Med. Ctr., Pennsylvania State Univ., Hershey, Pa.). Ann. Neurol. 3:438, 1978.

Three young adult patients are described to illustrate an uncommon syndrome, papillophlebitis. This entity, characterized by mild but protracted monocular visual impairment, edema of the optic disk, retinal venous engorgement, and perivenous retinal hemorrhages, resembles atherosclerotic occlusion of the central retinal vein in older patients. In younger individuals it is benign and self limited, but may be incorrectly diagnosed as optic neuritis or papilledema. These alternatives can usually be excluded if tests of visual function do not indicate an optic nerve conduction defect and if the clinical presentation and examination of the opposite ocular fundus do not disclose evidence of increased intracranial pressure. Because resolution usually occurs spontaneously, immediate neuroroentgenographic tests may be inappropriate. Effective treatment has not been established; local instillation of corticosteroids may hasten recovery. (1 figure, 8 references)—Authors' abstract

Archives of Dermatology

UVEITIS, POLIOSIS, HYPOMELANOSIS, AND ALOPECIA IN A PATIENT WITH MALIGNANT MELANOMA. Sober, A. J., and Haynes, H. A. (Massachusetts Gen. Hosp., Boston, Mass.). Arch. Dermatol. 114:439, 1978.

Bilateral uveitis, poliosis, hypomelanosis, and alopecia (Vogt-Koyanagi-Harada syndrome) developed spontaneously in a 57-year-old woman following operation for metastatic malignant melanoma. She has been disease-free for eight and one half years in spite of a highly unfavorable prognosis. Within the framework of current concepts of cell-mediated and humoral immunity in patients with malignant melanoma, activity of the host's immune system is postulated for the destruction of normal melanocytes in the skin, hair follicle, and uveal tract, as well as for the favorable outcome. (3 figures, 25 references)—Authors' abstract

Archives of Internal Medicine

SYSTEMIC FACTORS CONTRIBUTORY TO RETINAL VEIN OCCLUSION. McGrath, M. A., Wechsler, F., Hunyor, A. B., and Penny, R. (St. Vincent's Hosp., Darlinghurst, Australia). Arch. Intern. Med. 138:216, 1978.

This study was undertaken in 79 patients with retinal vein occlusion to assess the different systemic mechanisms contributing to the occlusion, namely, intrinsic vessel disease and abnormalities of the blood constituents and blood viscosity. In 55 patients older than 50 years of age, important associations were hypertension, abnormal results on glucose tolerance test, hyperlipidemia, chronic lung disease, and elevated serum IgA levels. In the 24 patients younger than 50 years of age, male incidence was high and important associations were head injuries, hyperlipidemia, and the use of estrogen-containing preparations. Hyperviscosity and cryofibrinogenemia were prominent in both groups. (3 figures, 2 tables, 32 references)—Authors' abstract

British Journal of Anaesthesia

INTRAOCULAR PRESSURE CHANGES DURING HALOTHANE AND ENFLURANE ANESTHESIA. Runciman, J. C., Bowen-Wright, M., Welsh, N. H., and Down-

ing, J. W. (Dept. Anesthesia, Univ. of Natal, Congella, South Africa). Br. J. Anaesth. 50:371, 1978.

The authors measured intraocular pressure in 20 patients anesthetized with halothane or enflurane for repair of trauma to the eye. The changes in intraocular pressure with halothane 0.5% were unpredictable, whereas enflurane 1% reduced intraocular tension consistently in all the patients studied. Enflurane is recommended as a possible alternative anesthetic for surgery on the open eye. (2 figures, 8 references)—Authors' abstract

British Journal of Ophthalmology

PATTERN OF AMBLYOPIA AND FIXATION AFTER KERATOPLASTY. Singh, G., and Das, P. N. (Dept. Ophthalmol., Maulana Azad Med. College and Irwin Hosp., New Delhi, India). Br. J. Ophthalmol. 62:29, 1978.

In 40 cases of clear corneal grafts, the visual acuities with the best optical correction were analyzed with respect to: (1) the age at which the patient's cornea had become scarred, (2) his or her age at the time of surgery, and (3) the fixation pattern at the final assessment of the visual result. The poorest results, i.e., severe, irreversible amblyopia with eccentric fixation, were observed in cases of unilateral scarring incurred before the age of five years and not repaired until the second or third decade of life. In cases of bilateral scarring sustained before the age of five, the corneal graft improved the vision of the eye with better preoperative acuity and foveal fixation. If the scarring had occurred after the age of five years, the visual results were good and not demonstrably dependent upon the time interval between the occurrence of the scarring and its repair. In most of these cases the final fixation pattern was foveal. The keratoplasties did not influence any strabismus present before the operation. (4 figures, 3 tables, 12 references)—Peter C. Kronfeld

HISTOPATHOLOGY OF HUMAN SUPERFICIAL HERPES SIMPLEX KERATITIS. Maudgall, P. C., and Minotten, L. (Dept. Ophthalmol., Catholic Univ., Leuven, Belgium). Br. J. Ophthalmol. 62:46, 1978.

The authors obtain specimens of corneal epithelium in cases of superficial keratitis by applying a 2.3% solution of collodion in amyl acetate to the dried corneal surface with a small, soft hair brush. The solvent evaporates quickly, leaving behind a thin, transparent film of collodion which can be lifted off with fine forceps and includes a layer of corneal epithelium. The entire film or parts of it are mounted on glass slides, with the epithelium side down. The collodion is dissolved with acetone, leaving the epithelial cells adherent to the slide which can then be treated by conventional staining methods. Preparations suitable for electron microscopy can be obtained by treating the film with glutaraldehyde and osmium tetraoxide. Experimental studies on rabbits have revealed no permanent damage to the cornea. The present paper describes and illustrates the authors' findings in 20 cases of superficial herpetic ulcers. The dendrites are composed of rounded epithelial cells and of syncytia made up of oddly shaped cell nuclei. Pseudopodia-like processes containing DNA and some RNA extend from the syncytia into the surrounding epithelial cells which, on coming in contact with these processes, become rounded and liquified, thus giving rise to another syncytium. The superficial cells surrounding the dendritic lesions are elongated and oriented parallel to the long axis of the lesion, assuming a more accurate orientation around the terminal bulbs of the dendrite. Polymorphonuclear leukocytes and lymphocytes are conspicuously absent from the preparations. (12 figures, 10 references)—Peter C. Kronfeld

British Medical Journal

HLA PATTERNS AND DIABETIC RETINOPATHY. Larkins, R. G., Martin, F. I., and Tait, B. D. (Royal Melbourne Hosp., Melbourne, Australia). Brit. Med. J. 1:1111, 1978.

Studies in diabetic identical twins have suggested that genetic factors may have a role not only in the liability to diabetes but also in the likelihood of diabetics developing retinopathy. The pattern of HLA antigens is genetically determined and the association between the HLA patterns and insulin-dependent diabetes has been well established. This investigation was aimed at seeking an association between the HLA pattern and liability to or protection from severe diabetic retinopathy in insulin-dependent diabetic patients.

There is a strong association between HLA antigens A1 and B8. Thus the pattern B8 without A1 is uncommon, occurring in only 4% of nondiabetic Caucasians. The current study shows a strong association between this unusual HLA pattern (B8 without A1) and severe proliferative retinopathy in insulin-dependent diabetic patients. This suggests that genetic factors linked to the HLA system have a dominant role in determining the development of, or protection from, diabetic complications. (1 table, 4 references)—David Shoch

Diabetes

QUANTITATIVE VITREOUS FLUOROPHOTOMETRY. A SENSITIVE TECHNIQUE FOR MEASURING EARLY BREAKDOWN OF THE BLOOD-RETINAL BARRIER IN YOUNG DIABETIC PATIENTS. Waltman, S. R., Oestrich, C., Krupin, T., Hanish, S., Ratzan, S., Santiago, J., and Kilo, C. (Washington Univ. School of Med., St. Louis, Mo.). Diabetes 27:85, 1978.

Vitreous and aqueous humor fluorescein concentrations were measured one hour after graded intravenous fluorescein was given to 20 juvenile diabetics, ages 20 to 40, with and without retinopathy, and to 12 controls of similar age. Vitreous fluorescein concentrations were significantly higher in diabetics, indicating breakdown of the blood-retinal barrier. Mean vitreous fluorescein values were 10.66 ± 0.65 for the diabetics and 4.28 ± 0.37 ng/ml for the controls. Breakdown of the blood-retinal barrier was also confirmed in diabetics under the age of 20 without retinopathy. The blood-aqueous barrier was similarly altered in diabetics. Vitreous fluorophotometry quantitatively measures breakdown of the blood-retinal barrier, possibly the earliest detectable ocular vascular abnormality in juvenile diabetic patients. (1 figure, 1 table, 3 references)—Authors' abstract

Journal Français d'Ophtalmologie

CONVENTIONAL LENSES AND CONTACT LENSES IN THE EVOLUTION OF MYOPIA. (French) Balacco-Gabrieli, C., Bellizzi, M., Salamanna S., and Scorcia, G. (Eye Clinic, Univ. of Bari, Bari, Italy). J. Fr. Ophtalmol. 1:283, 1978.

The authors divided 202 patients, all of whom had more than five degrees of myopia in one or both eyes, into three subgroups. The first group was treated with conventional glasses, the second group with hard contact lenses, and the third group with soft contact lenses. Each group was subdivided by age so that the first subgroup was from 16 to 20 years old, the second subgroup from 21 to 43, and the third subgroup from 43 to 75. In each group about two thirds of the patients in the youngest age interval progressed no matter what type of corrective device was prescribed. On the other hand, there was very little progression of myopia in the oldest age subgroup in each of the three divisions. Small variations were noted but when these were subjected to statistical analysis, there was no conclusive evidence that the use of contact lenses either slowed or stopped the progression of myopia. (11 references)—David Shoch

ENZYMATIC OCULAR HYPERTENSION: A STATISTICAL STUDY. (French) Menezo, J. L., Marco, M., and Mascarell, E. V. (Central Hosp., Valencia, Spain). J. Fr. Ophtalmol. 1:289, 1978.

Two groups of patients underwent similar cataract surgery except for the use of alpha-chymotrypsin in the first group of approximately 1,000 patients and the absence of the use of chymotrypsin in the second group of 324. The intraocular pressure was measured 24 to 48 hours after the surgery and regularly thereafter. The incidence of raised intraocular pressure when enzymes were used was 40.3% and when it was not used, 25.3%. This is a statistically significant difference. The ocular hypertension persisted for about three weeks. When the hypertension appeared did not vary materially in the two groups and the duration was not significantly different in the two groups either. Further, there did not seem to be any relationship between the level of ocular hypertension and the quantity of enyzme employed. (48 references)—David Shoch

METASTATIC TUMORS OF THE LIDS. (French) Auvert, B., Haye, C., Laurent, M., and Dufier, J. L. (Laënnec, Paris, France). J. Fr. Ophtalmol. 1:317, 1978.

Forty-seven patients with metastatic tumors of the lids were studied and the sites of origin determined. They were, in the following order

of frequency: breast (28 cases, 59%), malignant melanoma, six skin and one choroid, (7 cases, 25.5%), lung (6 cases, 13%), stomach (3 cases, 6.5%), miscellaneous, one each from the parotid, colon and thyroid (3 cases, 6.5%). (17 references)—David Shoch

Journal of Medical Genetics

LINKAGE RELATIONS OF A LOCUS FOR CONGENITAL TOTAL NUCLEAR CATARACT. Huntzinger, R. S., Weitkamp, L. R., and Roca, P. D. (Division of Genet., Univ. of Rochester School of Med., Rochester, N. Y.). J. Med. Genet. 15:113, 1978.

With the exception of zonular pulverulent cataract, no dominantly inherited congenital cataract has been found to be associated with any marker system. The present article reports a family with an autosomal dominant form of congenital total nuclear cataract. An examination was done for total linkage between the cataract and 30 marker loci. Close linkage was excluded for all of the 21 informative loci. There was no significant evidence for linkage of the cataract locus with any of the marker loci. (1 figure, 1 table, 7 references)—David Shoch

Journal of Pediatrics

PRIMARY MENINGOCOCCAL CONJUNCTIVITIS FOLLOWED BY MENINGITIS. Nussbaum, E., Jeyaranjan, T., and Feldman, F. (Dept. Pediatr., Maimomodes Med. Ctr., Brooklyn, N. Y.). J. Pediatr. 92:784, 1978.

The conjunctival sac is rarely the portal of entry for serious systemic infection. However, this can occur and it is reported here. Three days prior to the onset of systemic symptoms, a seven-month old child was seen with a severe purulent conjunctivitis. The conjunctiva was cultured and the patient given topical medication to use. On admission three days later, therapy was begun for *Neisseria meningitidis* on the basis of the conjunctival culture. The spinal fluid examination also grew this organism. It would seem appropriate to obtain smears of the exudate in severe cases of conjunctivitis in children. If gram-negative diplococci are identified, systemic therapy can be instituted in addition to local therapy. (6 references)—David Shoch

Mayo Clinic Proceedings

TREATMENT OF ACUTE CENTRAL RETINAL ARTERY OCCLUSION. Younge, B. R., and Rosenbaum, T. J. (Mayo Graduate School of Med., Rochester, Minn.). Mayo Clin. Proc. 53:408, 1978.

A 21-year-old man suddenly lost vision in his only good eye one hour following carotid angiography. Examination revealed a central retinal artery occlusion with typical "boxcarring" and many platelet-fibrin emboli. The usual treatments with anticoagulants and vasodilators were tried to no avail and therefore the patient was taken into the operating room and under general anesthesia a cut-down made on the supra-orbital artery and this artery irrigated in a retrograde fashion with heparinized saline followed by 20 mg of papaverine. Almost immediately the normal circulation of the fundus was restored. This was three and a half hours after the angiogram. Three hours later the vision had returned to pre-investigative levels, the edema of the disk had gone, as had the cherry red spot in the macula. There has been no further follow-up on this patient but the procedure is relatively simple, takes no sophisticated equipment and requires less than an hour of operating time. The authors appropriately point out that no conclusions can be drawn from one case but that this technique should be better known. (4 figures, 2 references)—David Shoch

New England Journal of Medicine

DIAGNOSIS OF TREATABLE WILSON'S DISEASE. Cartwright, G. E. (Dept. Med., Univ. of Utah College of Med., Salt Lake City, Utah). N. Engl. J. Med. 298:1347, 1978.

Wilson's disease may present in a variety of fashions. When it presents as either a neurologic disease or psychiatric disease, there is almost always a Kayser-Fleischer ring present and if this is present, no further diagnostic test is needed but penicillamine treatment should be started as soon as possible to present further deterioration of the patient. On the other hand, when the disease presents itself as liver failure or anemia, then it is more difficult to make the diagnosis, since the Kayser-Fleischer ring is usually not present. Wilson's disease is inherited as an autosomal recessive and since the gene is not common in the population,

most patients with the disease, who are homozygotes, will be the product of the marriage of two carriers – heterozygotes. On the average, 25% of the children of two heterozygotes can be expected to have the disease. Therefore it is most important to screen the siblings of any patient with established Wilson's disease. A simple ceruloplasmin determination will show decreased levels, or if need be, liver biopsy can be done to show an increased copper concentration in the liver. In essence, this is most commonly a treatable neurologic or psychiatric disease, whose diagnosis can be made by examination of the eyes. (16 references)—David Shoch

Ophthalmic Surgery

THE EFFECTIVENESS OF THE PIGTAIL PROBE METHOD OF REPAIRING CANALICULAR LACERATIONS. Saunders, D. H., Shannon, G. M., and Flanagan, J. C. (Wills Eye Hosp., Philadelphia, Pa.). Ophthalmic Surg. 9:33, 1978.

The authors were able to follow 30 patients who had had canalicular lacerations repaired by the use of a pigtail probe. The average follow-up time was 23 months and at the end of this time, only 11 of the 30 patients had a patent canalicular system, but significantly, of the 19 patients whose surgery failed, 14 remained asymptomatic and without complaint. The authors conclude that the pigtail probe-technique is not a good one for repairing caniculi since it frequently produces false passages and is difficult to manipulate. They suggest that this technique be abandoned and instead a canicular support technique be used such as a Veirs rod or a Johnson wire and that the canaliculus itself be repaired by end to end suturing with 8-0 or 9-0 silk. (5 figures, 6 tables, 20 references)—David Shoch

Ophthalmology

THE PHARMACOLOGY OF AMBLYOPIA. Duffy, F. H., Burchfiel, J. L., and Snodgrass, S. R. (Dept. Neurol., Children's Hosp. Med. Ctr., Boston, Mass). Ophthalmol. 85:489, 1978.

Physiologic and anatomic evidence has suggested an anatomic disconnection between the deprived eye and visual cortical neurons in cats made amblyopic by monocular deprivation. Clinical and visual-evoked response data suggest, however, that inhibition may play a major role in amblyopia. Accordingly, the authors intravenously administered anti-inhibitory compounds (biocuculline, ammonium ion, naloxone) to amblyopic cats and demonstrated a substantial restoration of binocular input to the visual cortex. Such pharmacologic reversal suggests that amblyopia is not an anatomically fixed lesion. (2 figures, 33 references)—Authors' abstract

DIFFUSE UNILATERAL SUBACUTE NEURORETINITIS. Gass, J. D. M., Gilbert, Jr., W. R., Guerry, R. K., and Scelfo, R. (Bascom Palmer Eye Inst., Univ. of Miami School of Med., Miami, Fla.). Ophthalmol. 85:521, 1978.

Thirty-six young healthy patients developed a peculiar clinical syndrome affecting only one eye. The early stage of the disease was characterized by visual loss, vitritis, mild papilledema, and successive crops of multiple, evanescent, gray-white, deep, retinal lesions. Over a period of many months there developed widespread, diffuse and focal depigmentation of the pigment epithelium, retinal arterial narrowing, optic atrophy, severe visual loss, and electroretinographic changes, A motile, subretinal round worm, probably a *Toxocara,* was observed in two patients. If in fact the parasite can be located in an area outside of the central macular area, photocoagulation can be used to destroy it since there is no evidence to date that this produces an exaggerated inflammatory response. If the worm cannot be located and destroyed by photocoagulation, a trial of both corticosteroids and antihelminthic agents is advisable if the disease is recognized in its early stages. Chances of involvement of the second eye are small. (9 figures, 26 references)—David Shoch

Plastic and Reconstructive Surgery

USE OF AN ENCIRCLING SILICONE RUBBER STRING FOR THE CORRECTION OF LAGOPHTHALMOS. Lessa, S., and Carreirao, S. (Dept. of Plastic and Reconstructive Surg., Pontificia Universidade Catolica do Rio de Janeiro Med. School, Rio de Janeiro, Brazil). Plast. Reconstr. Surg. 61:719, 1978.

A silicone rubber string, one millimeter in diameter, is inserted under the skin near the

lid margin in the upper and lower lids. This is inserted in a circular fashion, starting at the outer canthus, going across the upper lid under the medial canthal ligament and back through the lower lid to emerge again at the lateral canthus. At this point the silicone string is attached to the periosteum of the lateral orbital margin. (5 figures, 23 references)—David Shoch

Southern Medical Journal

OCULAR FINDINGS IN WHIPPLE'S DISEASE. Leland, T. M., and Chambers, J. K. (Dept. Ophthalmol., Univ. of South Carolina, Charleston, S. C.). South. Med. J. 71:335, 1978.

Intestinal lipodystrophy, first described by Whipple, is characterized by intestinal malabsorption, diarrhea, progressive weight loss, polyarthralgia, and neurologic disorders. The diagnosis is confirmed by finding accumulations of foamy macrophages containing PAS-positive phagosomes in jejunal biopsy. Gram-positive bacilli have been implicated as the causative agents, and antibiotics have reduced the fatality rate. Since 1968 it has been known that there is frequently ocular involvement in patients with Whipple's disease. This includes papilledema, vitreous hemorrhages, external ophthalmoplegia, and optic atrophy. The patient reported here had uveitis, glaucoma, superficial punctate keratitis, and a fibrovascular pannus involving the anterior chamber angles and corneal periphery in both eyes. It has been suggested that hypersensitivity explains the ocular involvement in Whipple's disease. The pathogenic organisms apparently invade the eye and establish a hypersensitivity antigen-antibody response. Macrophages containing PAS-staining granules identical to those present in the jejunal biopsy specimens have been found in the retina of patients having Whipple's disease and ocular symptoms. (2 figures, 1 table, 20 references)—David Shoch

NEURAL AND DURAL OPTIC NERVE MEASUREMENTS WITH A-SCAN ULTRASONOGRAPHY. Skalka, H. W. (Univ. Alabama, Birmingham, Ala.). South. Med. J. 71: 399, 1978.

Ultrasonography has been shown to be of great value in studying drusen, cupping, and elevation of the optic disk, as well as mass lesions of the orbital optic nerve. The author finds A-scan ultrasonography to be an accurate and simple method of measuring both the diameter of the retrobulbar optic nerve and the size of the subdural perineural space. The author finds the intervaginal space of the retrobulbar optic nerve to be uniformly enlarged in papilledema, optic nerve lesions, and endocrine orbitopathy. (3 figures, 2 references)—Author's abstract

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.

700 North Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least three months before the date of occurrence.

AMERICAN INTRA-OCULAR IMPLANT SOCIETY: LENS SYMPOSIUM

The American Intra-Ocular Implant Society will hold its annual Intraocular Lens Symposium at the Century Plaza Hotel in Los Angeles April 8-11, 1979. For further information, write Kenneth J. Hoffer, M.D., Chairman, P.O. Box 3140, Santa Monica, CA 90403.

RESEARCH TO PREVENT BLINDNESS, INC., AWARDS

Jules Stein, chairman of Research to Prevent Blindness, Inc., announced Daniel M. Albert, professor of ophthalmic pathology at Harvard Medical School, Boston, as the recipient of the second annual Research to Prevent Blindness—William and Mary Greve International Scholars Award. The $25,000 award, the largest given internationally in the field of ophthalmic research, is intended to advance the work of outstanding young M.D. or Ph.D. scientists who are exploring new concepts in sight saving. The award was given to Dr. Albert in consideration of his pioneering research in the causes and pathogenesis of ocular tumors, particularly retinoblastoma and malignant melanoma.

Dr. Stein also announced the recipients of two additional annual scholars awards of $10,000 each: Ronald E. Smith, associate professor of ophthalmology at the University of Southern California, Los Angeles, received the 1978 Research to Prevent Blindness—James S. Adams Scholars Award for his work in ocular histoplasmosis; Thom J. Zimmerman, associate professor of ophthalmology and pharmacology at Louisiana State University, for his research in glaucoma and timolol, the beta-adrenergic blocker.

STATE UNIVERSITY OF NEW YORK: 29TH ANNUAL POSTGRADUATE COURSE IN OPHTHALMOLOGY

The State University of New York will hold its 29th Annual Postgraduate Course in Ophthalmology Dec. 1 and 2, 1978. This year's program will emphasize pediatric ophthalmology, vitreoretinal disease, ocular pathology with clinical correlations in iris-corneal lesions, the macula, and glaucoma. For further information, write Program Assistant, Office of Graduate and Continuing Education, State University of New York, Upstate Medical Center, 750 East Adams St., Syracuse, NY 13210; telephone (315) 473-4607.

ESTELLE DOHENY EYE FOUNDATION: POSTGRADUATE CONFERENCE ON DIAGNOSTIC TECHNIQUES IN OPHTHALMOLOGY

The Estelle Doheny Eye Foundation and the University of Southern California Department of Ophthalmology will sponsor a postgraduate conference dealing with practical aspects of diagnostic techniques in ophthalmology Dec. 14-16, 1978, on the Health Sciences Campus of the University of Southern California Medical School, Los Angeles. Don Minckler will be conference director; Lorenz E. Zimmerman will give the Estelle Doheny Memorial Lecture on changing concepts in the treatment of melanomas. William F. Hoyt will give the Irvine Memorial Lecture on the vitreous connection. For more information, write S. William Dowey, Estelle Doheny Eye Foundation, 1355 San Pablo St., Los Angeles, CA 90033; telephone (213) 226-2751.

RUDOLPH ELLENDER MEDICAL FOUNDATION: 19TH ANNUAL INSTRUCTIONAL COURSE

The Rudolph Ellender Medical Foundation will present its 19th Annual Instructional Course in Contact Lens Fitting in New Orleans March 29 and 30, 1979. For further information, write Joseph A. Baldone, M. D., Rudolph Ellender Medical Foundation, Inc., Roof, Delta Towers, New Orleans, LA 70112.

UNIVERSITY OF MICHIGAN MEDICAL CENTER: OPHTHALMOLOGY CONFERENCE

The University of Michigan Medical Center Department of Postgraduate Medicine and Health Professions Education will sponsor an ophthalmology

conference May 10 and 11, 1979, at the Towsley Center, Ann Arbor, Michigan. For further information, write Floyd C. Pennington, Director, Office of Continuing Education, Towsley Center for Continuing Medical Education, University of Michigan Medical School, Ann Arbor, MI 48109.

University of Vermont: New Division of Ophthalmology

The University of Vermont College of Medicine has established a fulltime Division of Ophthalmology. Phil Aitken has been named chairman of the division as well as chief of the Ophthalmology Service at the Medical Center Hospital of Vermont.

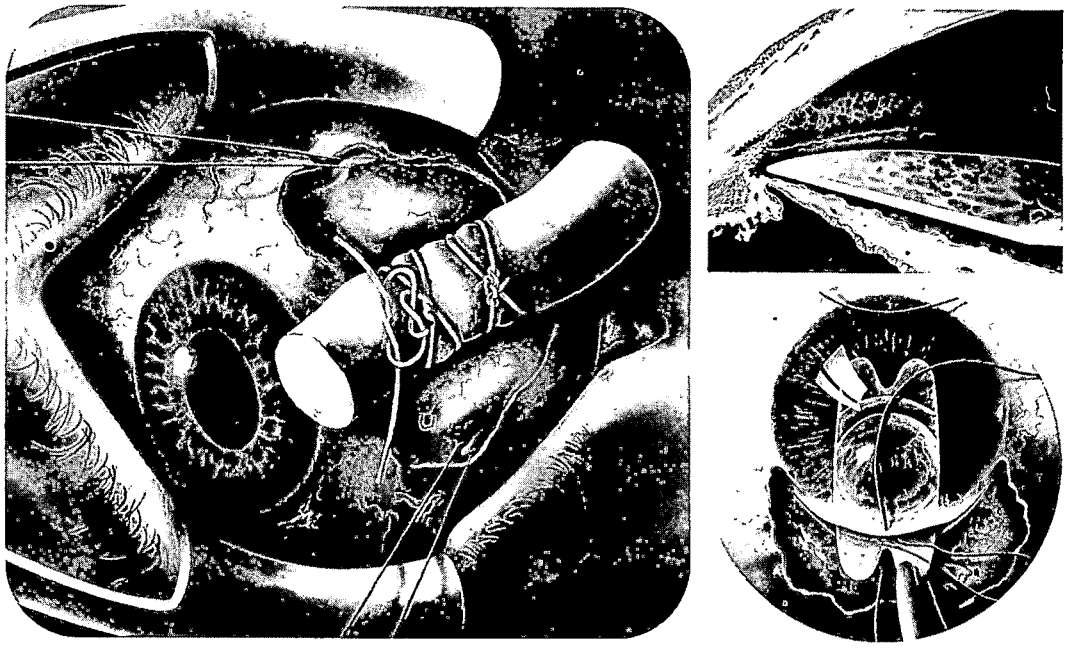
Miami Ophthalmological Society: Current Officers

The current officers of the Miami Ophthalmological Society for 1978–1979 are as follows: President, James C. Major; Secretary, David J. B. Singer.

National Eye Institute: Fellowship Program in Biometry and Epidemiology

The Office of Biometry and Epidemiology, National Eye Institute, in Bethesda, Maryland, offers a two-year pre- or postresidency ophthalmology fellowship in biometry and epidemiology. The fellowship includes participation in the planning, protocol development, and scientific administration of clinical trials and other epidemiological studies. The program provides for study in the following: the general principles of research; the methodology of clinical trials; basic statistics; the principles of epidemiology; and an introduction to the use of computors. About 70 to 80% of the time is spent obtaining practical experience in clinical trials and epidemiologic research with the other 20 to 30% allocated to the study program. A short training course in ophthalmology can be provided for those requiring it. Further, a limited amount of primary patient care responsibilities can be arranged.

For further information, write Karen Wright, Personnel Office, National Eye Institute, 9000 Rockville Pike, Bethesda, MD 20014; telephone (301) 496-4274.



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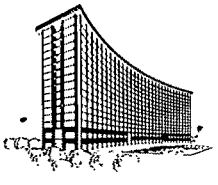
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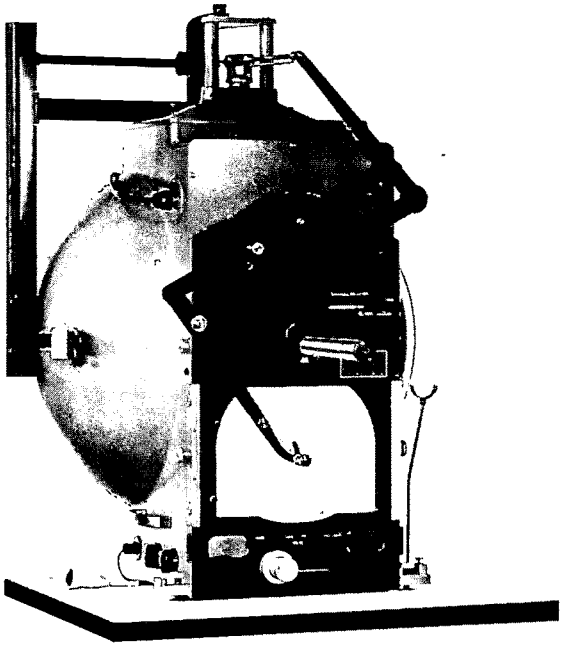
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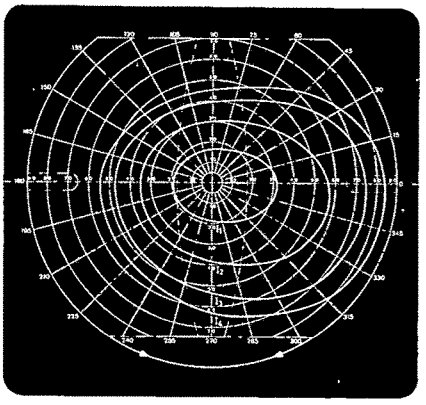
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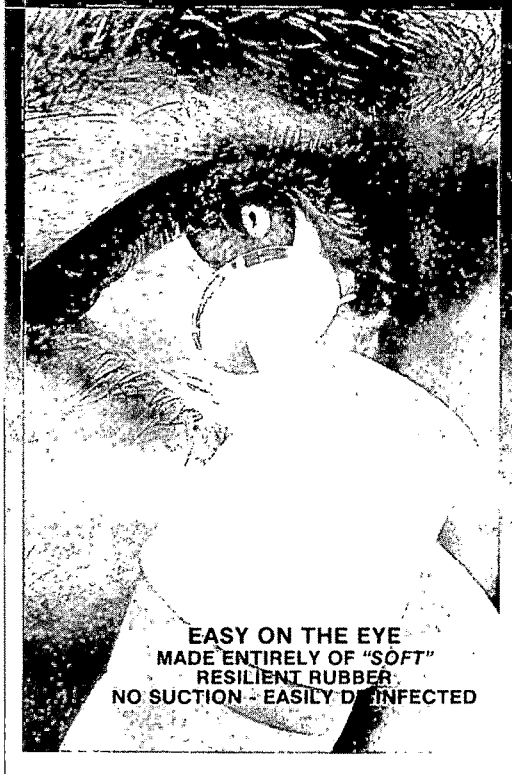
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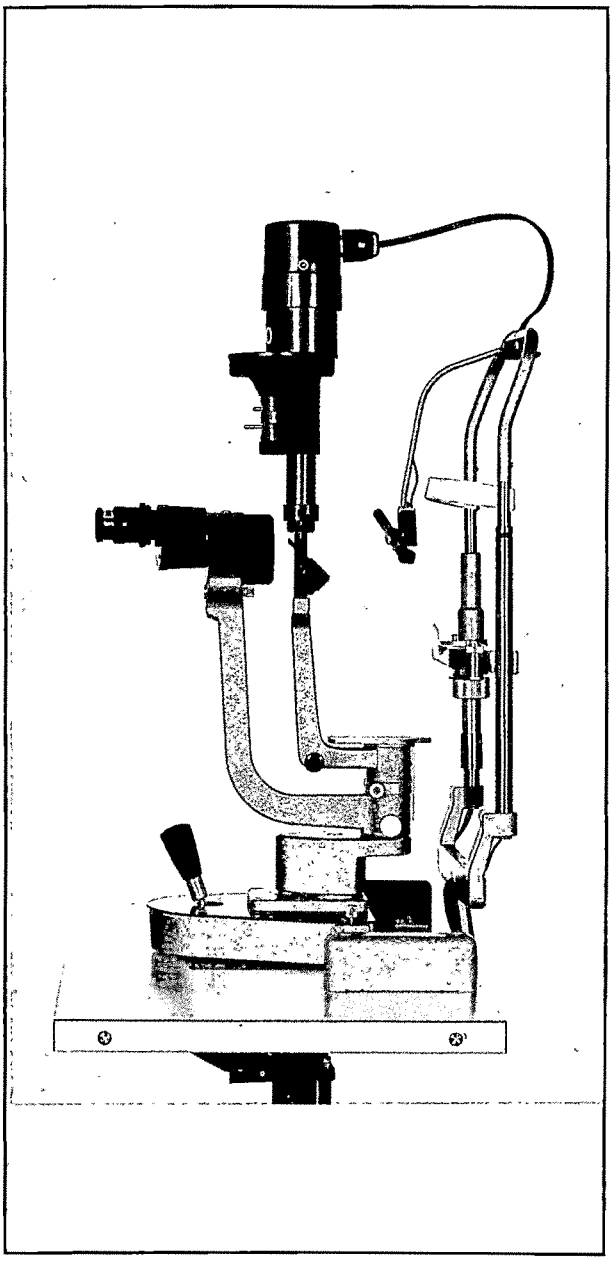
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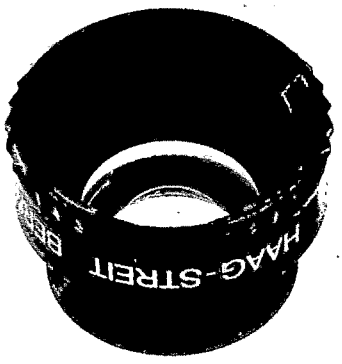
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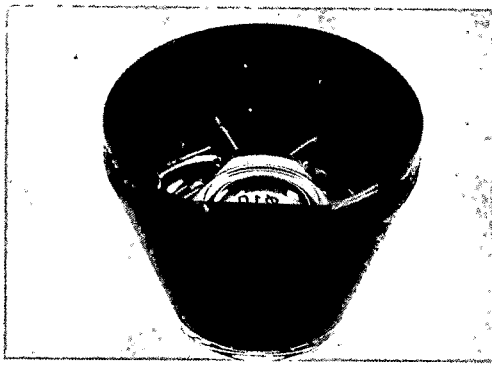
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Adverse Reactions: 1. Although the relationship, if any, of retinal detachment to the administration of PHOSPHOLINE IODIDE has not been established, retinal detachment has been reported in a few cases during the use of PHOSPHOLINE IODIDE in adult patients without a previous history of this disorder.
2. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.
3. Activation of latent iritis or uveitis may occur.
4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.
5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.
6. Lens opacities occurring in patients under treatment for glaucoma with PHOSPHOLINE IODIDE have been reported and similar changes have been produced experimentally in normal monkeys. Routine examinations should accompany clinical use of the drug.
7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.
Overdosage: Antidotes are atropine, 2 mg parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg per kg intravenously; artificial respiration should be given if necessary.
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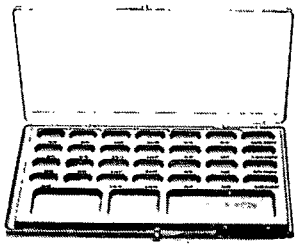
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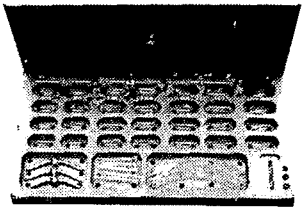
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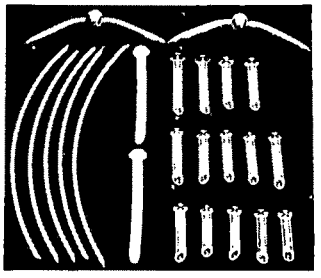
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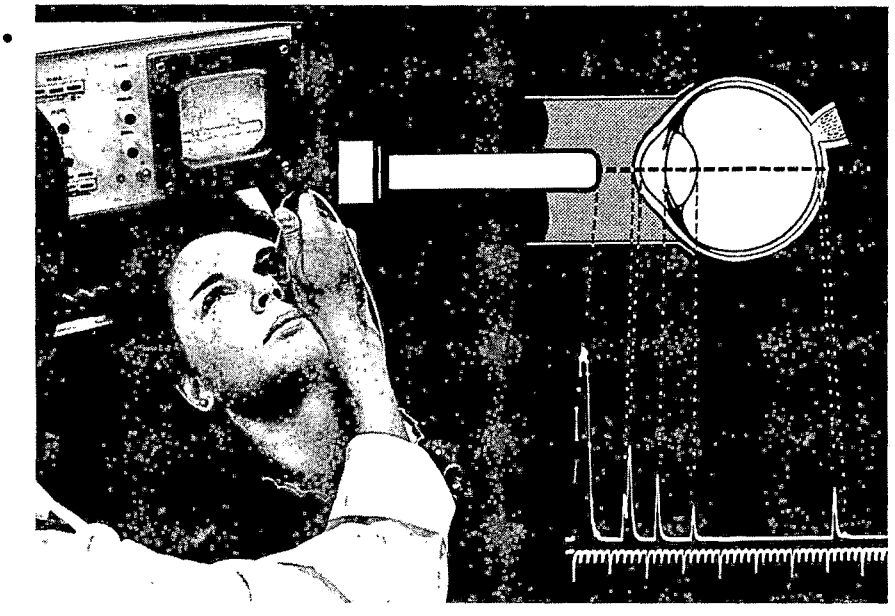
* L.T. Jones M.D., Dacryocystorhinostomy, American Journal of Ophthalmology, Volume 59, No. 5, May, 1965.
J.C. Mustarde', L.T. Jones M.D. and A. Callahan M.D., Ophthalmic Plastic Surgery---Up-To-Date, Aesculapius Publishing Company, 1970.
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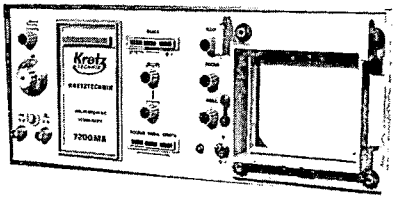


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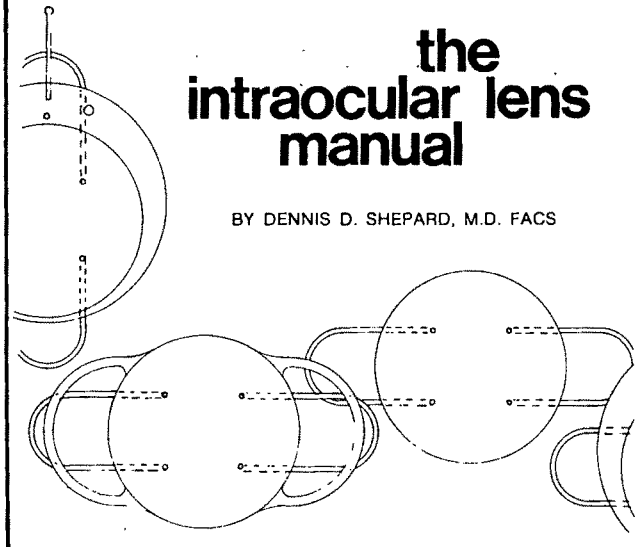
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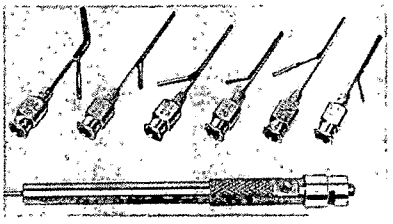
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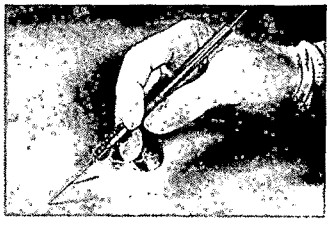
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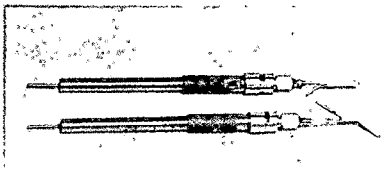
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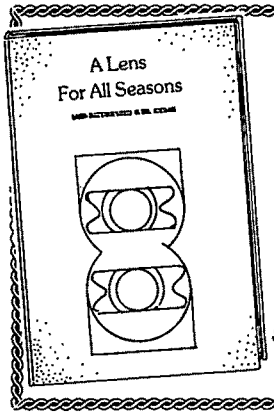
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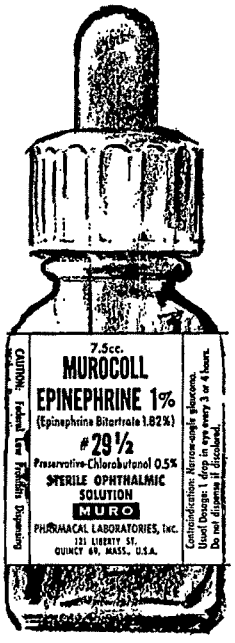
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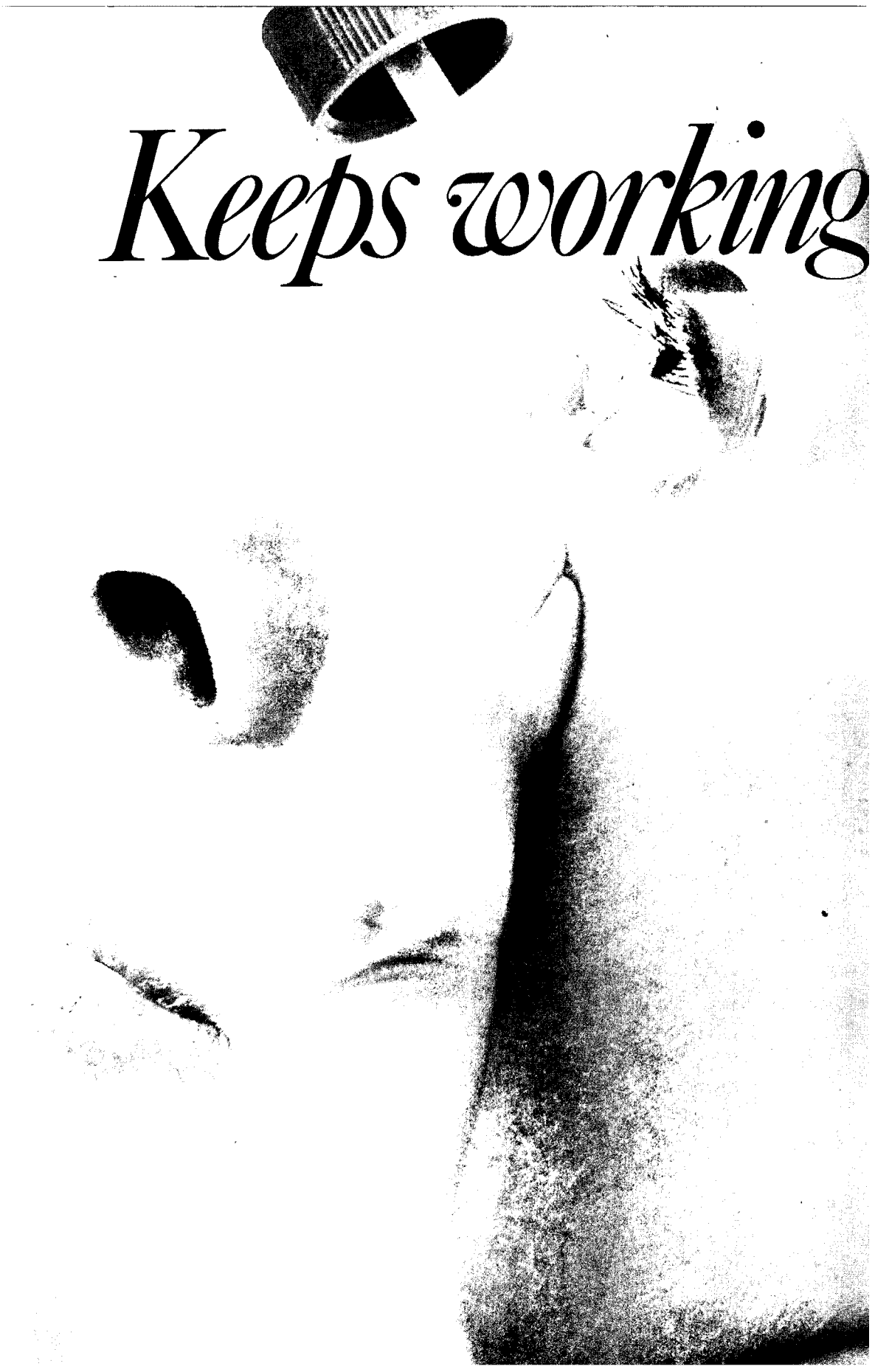
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8. PHOSPHOLINE IODIDE (echothiophate iodide) should be used with great caution, if at all, where there is a prior history of retinal detachment.
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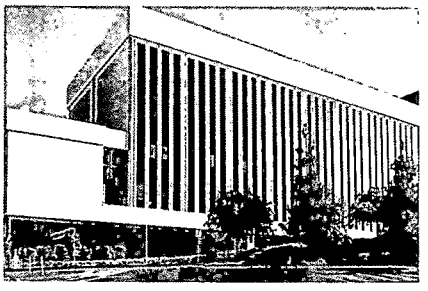
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Friday: Radiological Techniques in Orbital Diagnosis, Computerized Tonography, Ultrasound & Doppler in Orbital Diagnosis, Laboratory Diagnosis of Thyroid Disease, Drugs in Ocular Diagnosis, Background, Basics & Perspectives in Fluorescein Angiography, Retinal Vascular Disease, Diabetes, Intraocular Tumors, Iris Angiography, Macular Diseases,

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Tuition: $250 (includes course abstract, luncheons, social hours, coffee breaks and dinner dance).

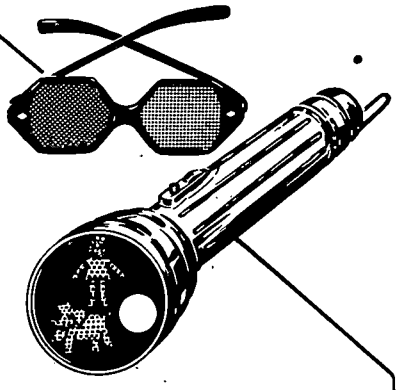
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Course Directors: Charles A. Garcia, M.D. and Jack T. Holladay, M.D.
The Annual Ophthalmology Board and Recertification Review course
will begin at 7:00 a.m., Monday, December 4
and end at 5:30, Friday, December 8.
Lunch will be served each day.

Tuition: $500.00

For further information, contact:
Board Review

Department of Ophthalmology
Hermann Eye Center
Hermann Hospital
1203 Ross Sterling
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Phone: (713) 797-1777

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INTERESTED PARTIES
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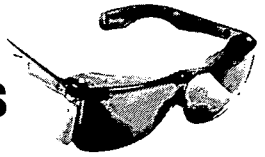
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OCTOBER 13, 1978

"HOW TO FIT A PATIENT STEP BY STEP"

Taking Measurements — Insertion and Removal
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Ordering Lenses — Assessing the well-fitted Lens
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LECTURERS

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Frank B. Hoefle, M.D. — **James J. Koverman**
Craig Iwig

This course is designed for ophthalmologists desiring to start a fitting program; and technicians sponsored by ophthalmologists.

Registration fee: $75.00 — Limited enrollment

AMA-CME Credit in Category 1: 8

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New York Eye and Ear Infirmary
310 East Fourteenth Street
New York, New York 10003

9TH ANNUAL COURSE OF THE EDWARD S. HARKNESS EYE INSTITUTE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY NOVEMBER 16 & 17, 1978

ADVANCES IN OCULAR THERAPEUTICS

14 hours of credit in Category 1 of the Physician's Recognition Award of the American Medical Association

The meeting will focus on recent advances in chemotherapy of ocular diseases. The speakers will include many experts in the non-surgical treatment of eye disease. The following areas will be covered: the treatment of ocular infection, ocular inflammation and allergy, use of medications in strabismus, a critical assessment of new drugs in the treatment of glaucoma, medical treatment of retinal vascular disease and ocular tumors, the medical treatment of neuro-ophthalmic diseases, the medical management of corneal disease, and relevant current information on local and general anesthesia.

Registration fee, $200; ESHEI Alumni $100; resident $100 (with letter from Director of Department). For further information and application forms, please write to:

DR. ELIZABETH C. GERST, *Director*
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A position is available for a second and a third year resident in Ophthalmology at the Department of Ophthalmology, Louisiana State University. For further information contact Herbert E. Kaufman, M.D., Head, Department of Ophthalmology, L.S.U. Eye Center, 136 South Roman Street, New Orleans, La. 70112, telephone (504) 568-6700.

FLORIDA MIDWINTER SEMINAR IN OPTHALMOLOGY

February 5-7, 1979

Americana Hotel
Miami Beach, Florida

The Cataract Operation

This Seminar is designed to assist the practicing ophthalmologist in giving informed consent and rendering second opinions; to review the complications of cataract surgery, the problems of aphakia; to discuss newer methods to compensate for aphakia; review recent surgical techniques their indications, complications compared with "standard" intracapsular cataract extraction; review medical screening, anesthesia screening and "sitter" anesthesia.

FACULTY

John Clarkson, M.D. Miami, Florida	Roger Hiatt, M.D. Memphis, Tennessee
Nancy Davis, M.D. Miami, Florida	David Kasner, M.D. Miami, Florida
Richard K. Forster, M.D. Miami, Florida	Warren Lieberman, M.D. Miami, Florida
Antonio Gassett, M.D. Gainesville, Florida	Frank Polack, M.D. Gainesville, Florida
Edward Gelber Miami, Florida	Sigmund Rosen, M.D. Miami, Florida

The Florida Midwinter Seminar in Ophthalmology & Otolaryngology is co-sponsored by the University of Florida College of Medicine (Gainesville), the University of Miami School of Medicine (Miami), and the University of South Florida College of Medicine (Tampa). The program is accredited by the Council on Medical Education of the American Medical Association, Category I of the Physician's Recognition Award. Registration fee is $150 for practitioners and $50 for residents upon application from their Department Head. Mail registration fee (U.S. dollars only), payable to "Florida Midwinter Seminar", 405 Northeast 144th Street, Miami, Florida 33161. Special reduced rates have been arranged with the Americana Hotel, 9701 Collins Avenue, Miami Beach, Florida 33154.

VITRECTOMY SYMPOSIUM

New York Medical College
Department of Ophthalmology

November 17 and 18, 1978 • Barbizon Plaza Hotel
106 Central Park South, New York, N.Y. 10019

This course is for the general ophthalmologist.

A distinguished panel of vitreoretinal surgeons will discuss: the current indications and mode of treatment for anterior segment vitreous complications, lens removal, trauma of the anterior and posterior segment, complications of diabetic retinopathy, complicated retinal detachment and endophthalmitis. Diagnostic evaluation of the eye with diseased vitreous and retina will be discussed along with recent developments in vitreous physiology.

Faculty

Endre Balazs, M.D.
D. Jackson Coleman, M.D.
Nicholas Douvas, M.D.
J. Wallace McMeel, M.D.
Ronald G. Michels, M.D.
Gholam Peyman, M.D.
Charles Schepens, M.D.
Michael W. Dunn, M.D.
Danny H. Kaufman, M.D.
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Danny H. Kaufman, M.D.
Director, Vitreoretinal Service
New York Medical College
Program Chairman

Michael W. Dunn, M.D.
Professor and Chairman
Department of Ophthalmology
New York Medical College

Registration Fee $200.00 (Residents and Fellows $125)
For registration information please contact:
DANNY H. KAUFMAN, M.D.
1 Stone Place, Bronxville, N.Y. 10708

As an organization accredited for continuing medical education, New York Medical College certifies that this continuing medical education activity meets the critera for 11 credit hours in Category I of the Physician's Recognition Award of the American Medical Association.

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Experience in medical and surgical vitreo-retinal diseases.

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Washington Hospital Center
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NOVEMBER 3 & 4, 1978

BRYAN MEMORIAL HOSPITAL
LINCOLN, NEBRASKA

Midwest Intraocular Lens Implantation and Micro-Surgery Course

Course sponsor and director: Aziz Y. Anis, M.D.
Co-sponsor: Scientific Sessions Committee of the Nebraska Medical Association

Faculty

John J. Alpar, M.D. Amarillo, Texas	F. Thomas Ellingson, M.D. Bismarck, North Dakota	Marvin L. Kwitko, M.D. Montreal, Quebec, Canada	Dennis D. Shepard, M.D. Santa Maria, California
Aziz Y. Anis, M.D. Lincoln, Nebraska	John E. Gilmore, M.D. Santa Monica, California	David J. McIntyre, M.D. Bellevue, Washington	Charles W. Simcoe, M.D. Tulsa, Oklahoma
Donald E. Dickerson, M.D. Santa Monica, California	Herbert Gould, M.D. White Plains, New York	Stephen A. Obstbaum, M.D. New York, New York	Kazimirs Stivrins, M.D. Lincoln, Nebraska
David D. Dulaney, M.D. Sun City, Arizona	Henry Hirshman, M.D. Long Beach, California	Stephen Shearing, M.D. Las Vegas, Nevada	Larry W. Wood, M.D. Lincoln, Nebraska

This course is meant to teach the surgeon the principles and latest advanced techniques of implantation of the various intraocular lens designs. Different schools of thought are represented to give the course an overall objective attitude. The course will comprise of: observation of live surgery and video-tapes of different techniques, observation of short and long term post-operative patients, didactic session, practical session with animal and cadaver eyes with the operating microscope. Participants will receive the Shepard Intraocular Lens Manual as part of the registration fee.

Topics

1. History of IOL manufacture.
2. Indications and contraindications.
3. Pre and post operative care.
4. Calculations of IOL power.
5. Techniques of implantation of the Anis, Binkhorst, Choyce, Fyodorov, Shearing, and Worst-Medallion Lenses.
6. Intracapsular and extracapsular techniques.
7. Secondary implants.
8. Intraoperative difficulties and post operative complication.
9. The value of anti-prostaglandins and nutrient irrigating solutions.
10. New surgical instruments for new techniques.
11. Corneal problems with IOL and specular microscope studies of corneal endothelium.
12. Retinal and vitreous problems with IOLs and their management.

"As an organization accredited for continuing medical education, the Scientific Sessions Committee of the Nebraska Medical Association certifies that this continuing medical education offering meets the criteria for no less than 18½ hours of credit in Category I of the Physician's Recognition Award of the American Medical Association, provided it is used and completed as designed."

FEE $550 RESIDENTS $300

Make check payable to Midwest Intraocular Lens Implant Course. Registrations must be in our office before October 15, 1978.

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Address _____

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Phone ( ) _____
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I would like Hilton reservations. (Hilton Limousine Service to & from Airport provided)

Single $27 ☐ Double $35 ☐ Thurs. Nov. 2 ☐ Fri. Nov. 3 ☐ Sat. Nov. 4 ☐

Date of arrival _____ Time of arrival _____

Date of departure _____ Time of departure _____

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Mail check and registration to A. Y. Anis, M.D., 100 No. 56th Street, Suite 303, Lincoln, Ne. 68504

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Sponsored by
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NOVEMBER 2-3, 1978

FACULTY
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These films depict the normal anatomy and signs of ocular contusion as shown in scenes of the living fundus together with the Stenstrom cine.

Running Time: Indirect Ophthalmoscopy—41 minutes
16 mm sound
Contusion Injury—20 minutes
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For information contact: Retinal Service
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1 Day Workshop — (Fridays only)

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8:30-9:30 am	— Basic Introduction to Lens and Techniques
9:30-11:00 am	— Surgical Demonstration Lydia Hall Hospital 4 cases
11:00-12 Noon	— Post-op Examination of previously operated patients
12 Noon-1:00 pm	— Lunch and Discussion
2:00-4:00 pm	— Laboratory Practice
4:00-5:00 pm	— Discussion

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December 2, 1978

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February 3, 1979

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April 7, 1979

6 Hours Credit, per session, Category 1 AMA Physician's Recognition Award

$75.00 each session, Residents & Fellows $15.00 each session with letter from the Director of Department.

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THE POST GRADUATE INSTITUTE OF THE NEW YORK EYE AND EAR INFIRMARY
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310 East Fourteenth Street
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December 26, 1978 to January 1, 1979
Condado Hilton, Puerto Rico
University of Puerto Rico—Mercy Hospital

Aphakia

Rehabilitation of the Cataract Patient
Aphakic Glasses
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Intraocular Lenses

The symposium will be organized to bring together acknowledged authorities in the three disciplines of aphakia rehabilitation. Controversial topics will be explored together with recognized techniques to determine the safe method for treating the cataract patient.

Free papers related to the three topics are invited. This course is approved for Credit hours towards Category 1 of the AMA Physicians Recognition Award.

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Aphakic Spectacles Drs. M.N. Miranda, O.H. Dabazies, G.P. Halberg

Extended Wear Contact Lenses Drs. W. Townsend, R. Morrison, H.A. Stein

Extracapsular Surgery Drs. L.E. Katzen, J. Hartstein, H. L. Gould

Additional Faculty will be announced at a later date.

Registration Fee $200.00. For information please write
Stuart Haman and L.E. Katzen, M.D.
333 St. Pauls Place, Baltimore, Maryland 21202

Interested parties are advised to make travel arrangements with Travel Whirl Inc., 1301 York Road, Lutherville, Maryland 21208

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JULES STEIN EYE INSTITUTE
and
THE DEPARTMENT OF OPHTHALMOLOGY
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For each surgical Course and Workshop, the Institute provides appropriate major surgical equipment (e.g., phacoemulsification units, vitrectomy instruments, and photocoagulators); special items such as intraocular lenses, surgical microscopes, practice eyes, and mannequins; and customary supplies such as sutures, irrigating fluids, and sponges. Prior to each program, participants will receive recommended detailed information regarding the required personal surgical instruments, pre-program reading, and other aspects of the program.

The programs listed here are presented in conjunction with UCLA Extension, Department of Continuing Education in Health Sciences, and are approved for Category 1 credit by the CMA and AMA.

OPHTHALMIC SURGERY PROGRAMS

September 23, 1978 Cataract Surgery and Intraocular Lens Implantation Workshop .....Enrollment fee: $225.00 (15 participants)
Chairman: Bradley R. Straatsma, M.D., Charles R. Barnes, M.D., Kenneth J. Hoffer, M.D., Howard H. Stone, M.D., Murry K. Weber, M.D.

October 14, 1978 Photocoagulation Therapy Workshop .....Enrollment fee: $200.00 (20 participants)
Chairman: Stanley M. Kopelow, M.D., Barry M. Kerman, M.D., Alan L. Norton, M.D., John R. Privett, M.D.

November 18, 1978 Glaucoma Surgery Workshop .....Enrollment fee: $200.00 (15 participants)
Chairman: Robert E. Christensen, M.D., Kenneth J. Hoffer, M.D., Timothy V. Scott, M.D., Roger W. Sorensen, M.D., Howard H. Stone, M.D.

December 2, 1978 Corneal Surgery Workshop .....Enrollment fee: $200.00 (15 participants)

December 2, 1978 Corneal Surgery Workshop .....Enrollment fee: $200.00 (15 participants)
Chairman: Thomas H. Pettit, M.D., Patricia E. Bath, M.D., C. Richard Elander, M.D., Jeremy E. Levenson, M.D.

January 27, 1979 Ophthalmic Plastic Surgery .....Enrollment Fee: $200.00 (20 participants)
Chairman: Henry I. Baylis, M.D.,Robert E. Bartlett, M.D., David F. Kamin, M.D., Norman Shorr, M.D.

February 23 & 24, 1979 Phacoemulsification Surgery Course, ...Enrollment Fee: $300.00 (20 participants)
Chairman: Alan L. Shabo, M.D., Robert E. Christensen, M.D., Jeremy E. Levenson, M.D., James W. McKinzie, M.D., Thomas H. Petit, M.D., George B. Primbs, M.D.

March 17, 1979 Cataract Surgery and Intraocular Lens Implantation Workshop, ...Enrollment Fee: $225.00 (15 participants)
Chairman: Bradley R. Straatsma, M.D., Charles R. Barnes, M.D., Kenneth J. Hoffer, M.D., Howard H. Stone, M.D., Murry K. Weber, M.D.

May 26, 1979 Retinal Surgery Workshop .....Enrollment Fee: $200.00 (15 participants)
Chairman: Allan E. Kreiger, M.D., Barry M. Kerman, M.D., Bradley R. Straatsma, M.D., and Faculty

June 9, 1979 An Update of Pediatric Ophthalmology .....Enrollment Fee: $75.00 (Enrollment Limited)
Chairman: Arthur L. Rosenbaum, M.D., Leonard Apt, M.D., Bernard S. Davidorf, M.D., William L. Gaffney, M.D., Stephen S. Seiff, M.D., Roger W. Sorrenson, M.D., Sidney J. Weiss, M.D.

A 10% service charge will be withheld on all cancellations. Cancellations must be received in this office 30 days prior to Workshop.

.....

Please indicate Workshop(s) preferred:

_____ Date _____

_____ Date _____

I am enclosing my check in the amount of $ _____ for enrollment in the Workshop(s) indicated above. I understand I will receive confirmation of my enrollment by return mail, or in the event the Workshop is filled, that my check will be returned.

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Department of Ophthalmology
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December 7 and 8, 1978, at the
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Residents/Alumni Meeting
December 9, 1978

Faculty

Claes H. Dohlman, M.D.,
Boston, Massachusetts
Stuart I. Brown, M.D.,
Pittsburgh, Pennsylvania
Peter R. Laibson, M.D.,
Philadelphia, Pennsylvania
Richard H. Keates, M.D.,
Columbus, Ohio

For application, please write to: F. Phinizy Calhoun, Jr., M.D. 1365 Clifton Road, N.E., Atlanta, Georgia 30322

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For further information contact: Extended Programs in Medical Education, University of California, Room 569-U, Third and Parnassus Avenue, San Francisco, California 94143 or call (415) 666-4251.

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This course will present a practical approach to Neuro ophthalmology and qualifies for 16 credits in Category 1 for the AMA-CME Physicians' Recognition Award. The course will be augmented with slides and films of actual cases.

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OPHTHALMIC MICROSURGERY COURSE

NOVEMBER 1978

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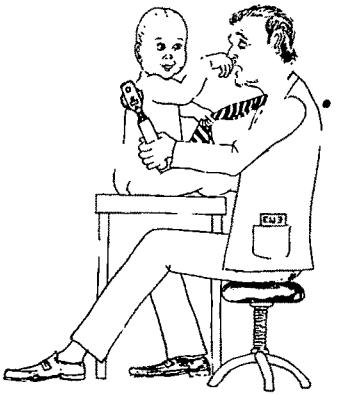
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For further information write or telephone: **Division of Ophthalmology**, Box 58, State University of New York, Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, New York 11203 (212) 270-1961.

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November 29—December 1, 1978



This course is meant to focus on some of the current problems and controversies in pediatric ophthalmology. The course will be divided into five half day sessions each one of which will concentrate on a subspecialty interest area within pediatric ophthalmology. The session topics will include:

Retrolental fibroplasia and retinal disease in children
Cataracts and glaucoma
Strabismus
Pediatric neuro-ophthalmology
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The purpose of the course is to provide the participant with the data necessary for him to re-evaluate his own understanding and treatment program in the above areas.

This program is presented by the Department of Ophthalmology and Extended Programs in Medical Education, University of California School of Medicine, San Francisco, California. This continuing medical education offering meets the criteria for 15 credit hours in Category I of the Physician's Recognition Award of the American Medical Association and the Certification Program of the California Medical Association.

The program will be held at the Plaza Square Ballroom, Hyatt Hotel on Union Square in San Francisco. The fee is $225.00. For further information please contact: Extended Programs in Medical Education, Room 569-U, University of California, San Francisco, California 94143 or call (415) 666-4251.

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PATHOLOGY I (4 hours)	Myron Yanoff, M.D., Chairman, Department of Ophthalmology, University of Pennsylvania, Director of Scheie Eye Institute
PATHOLOGY II (4 hours)	Myron Yanoff, M.D.
STRABISMUS (4 hours)	Robert D. Reinecke, M.D.,Professor and Chairman, Department of Ophthalmology, Albany Medical College of Union University
CORNEA AND EXTERNAL DISEASES (4 hours)	Juan Arentsen, M.D., Assistant Professor, Jefferson University; Associate Director, Cornea Service, Wills Eye Hospital
PHARMACOLOGY AND THERAPEUTICS (4 hours)	Joel S. Mindel, M.D., Assistant Professor, Department of Ophthalmology, Mt. Sinai School of Medicine
GLAUCOMA AND METABOLIC DISEASES (4 hours)	Stephen M. Podos, M.D., Professor and Chairman, Department of Ophthalmology; Mt. Sinai School of Medicine
EMBRYOLOGY & ANATOMY (4 hours)	David M. Worthen, M.D., F.A.C.S., Professor and Head, Division of Ophthalmology, University of California San Diego
MEDICAL OPHTHALMOLOGY (4 hours)	Paul Henkind, M.D., Ph.D., Professor and Chairman, Department of Ophthalmology, Montefiore Hospital and Medical Center
BANQUET SPEAKER	Bruce E. Spivey, M.D., Professor and Chairman, Department of Ophthalmology, Pacific Medical Center

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DEPARTMENT OF OPHTHALMOLOGY

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University of Wisconsin
Madison, Wisconsin

Melvin Chertack, M.D.
Lutheran General Hospital
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And faculty of the University of Illinois.

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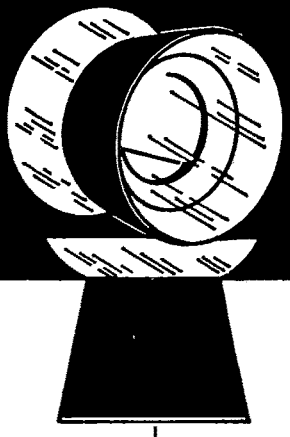
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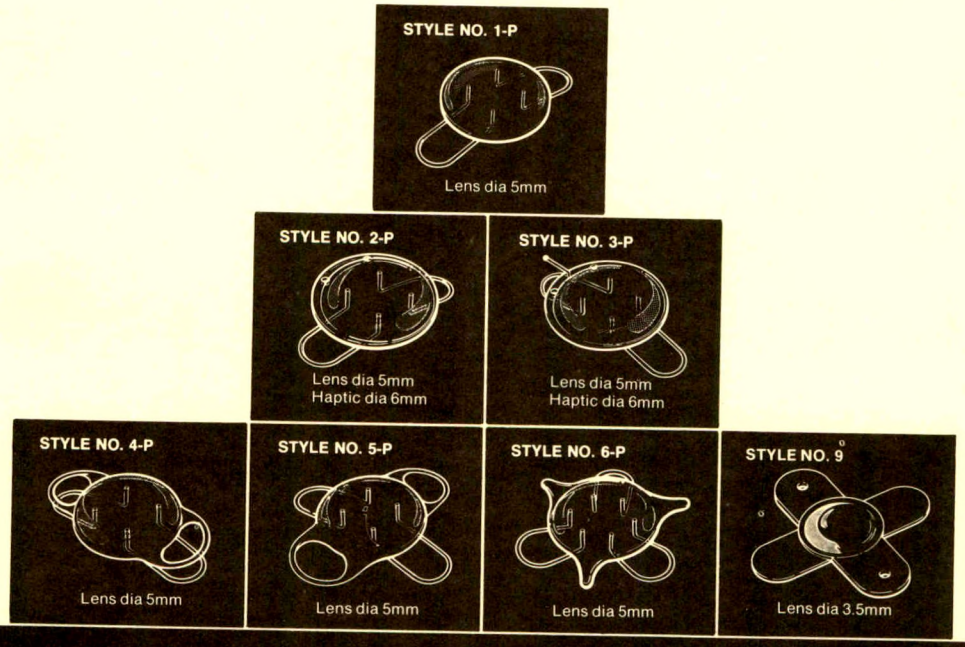
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REFERENCE NOTES:

1. Allergan Report Series, #72.
2. Hull, D.S. et al. Permeability of the isolated rabbit cornea to corticosteroids. Invest Ophthalmol 13, 457-459, 1974.
3. Fairbain, W. D. and Thorson, J. C. Fluorometholone—anti-inflammatory and intraocular pressure effects. Arch Ophthalmol 86: 138-141, 1971.

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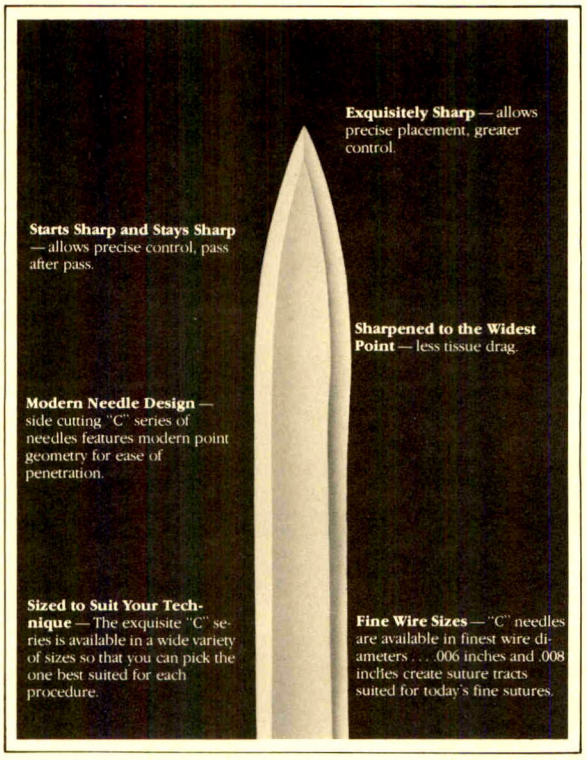
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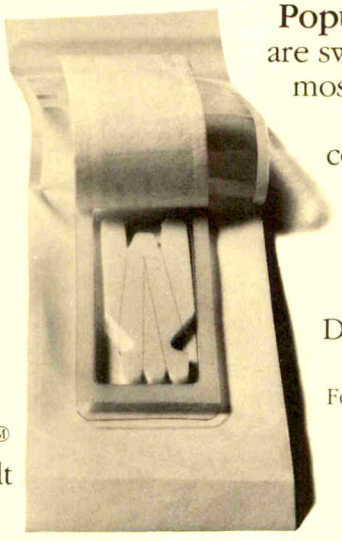


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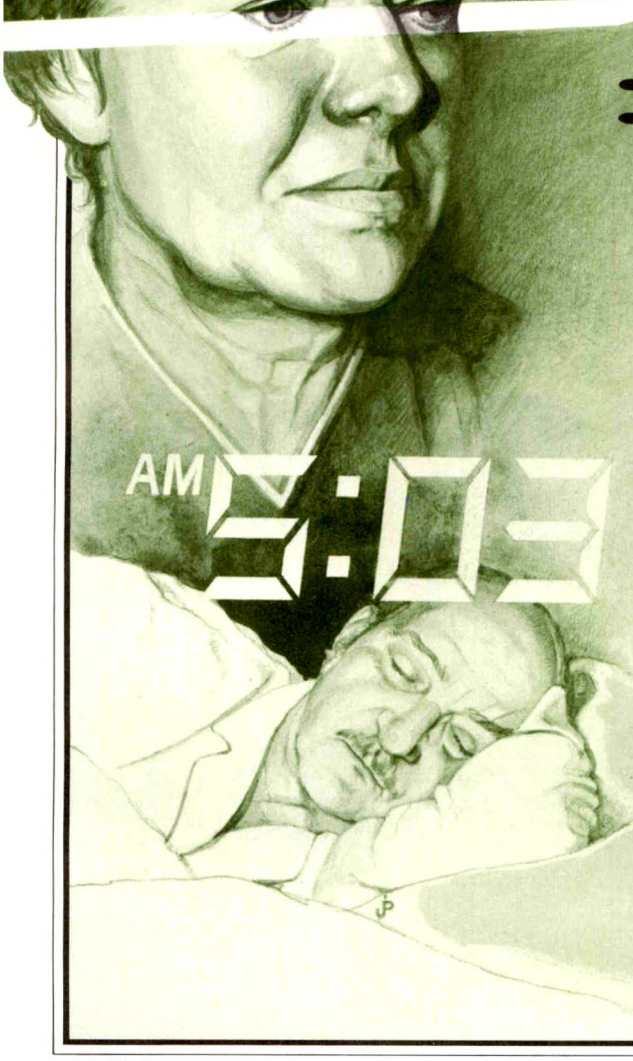
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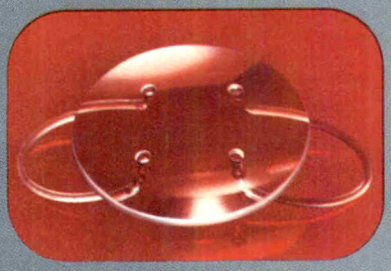
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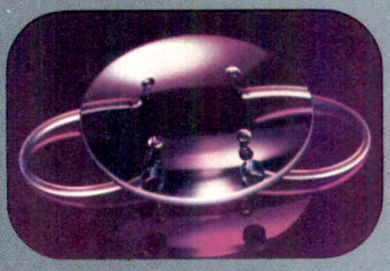
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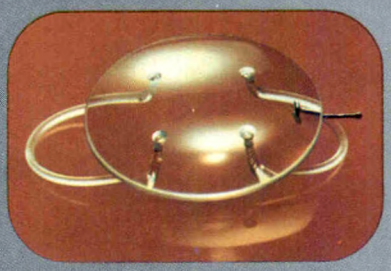
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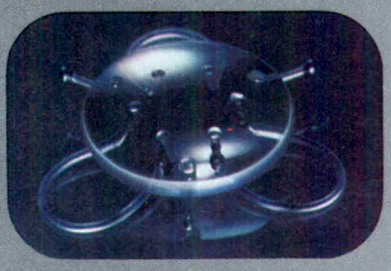
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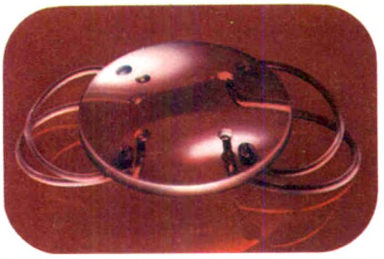
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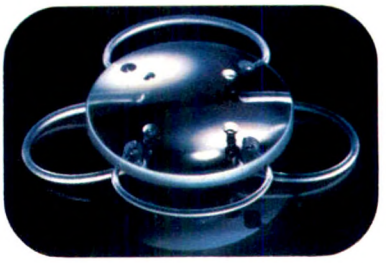


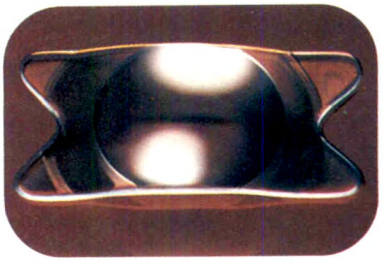












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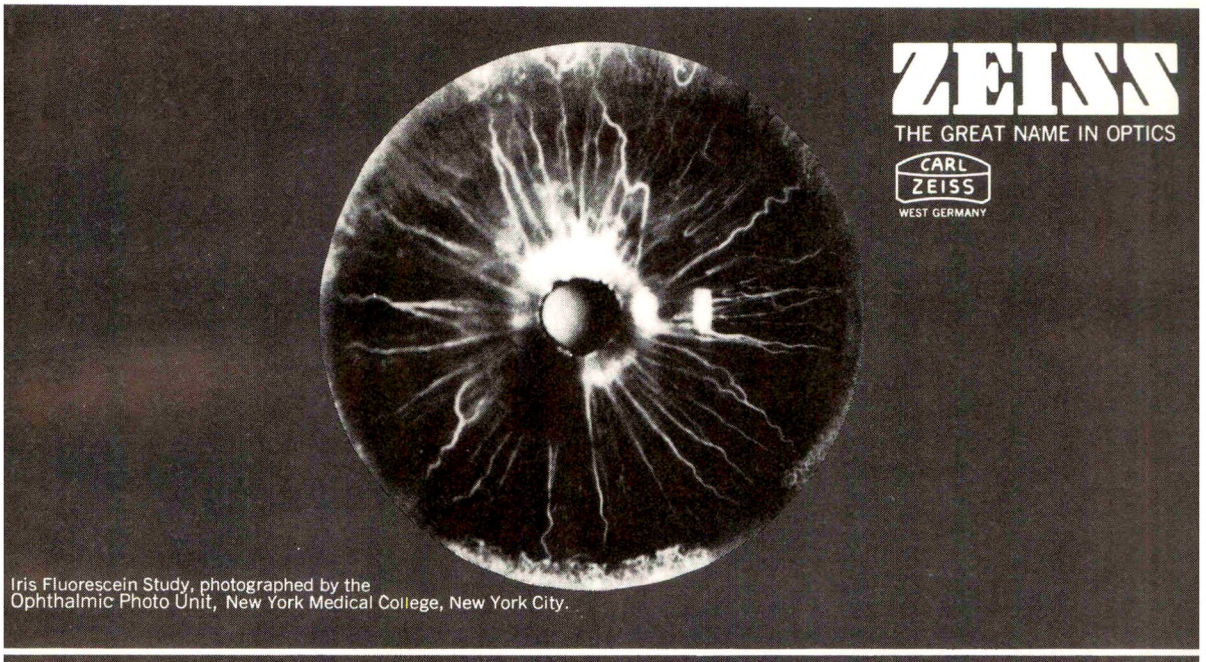
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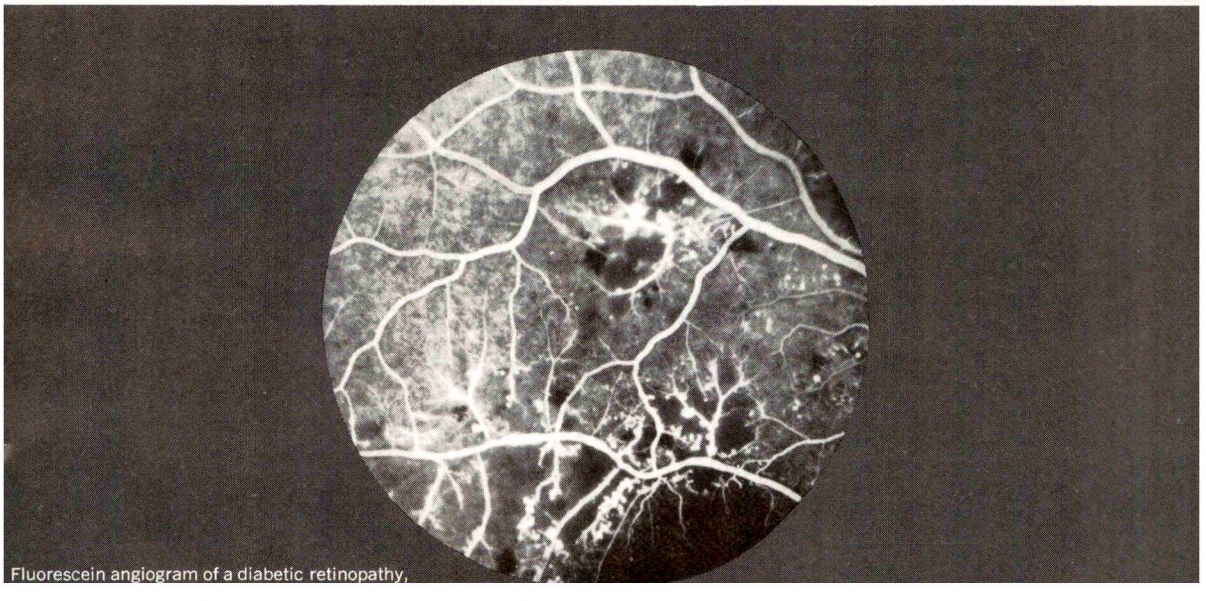
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Fluorescein angiogram of a diabetic retinopathy.

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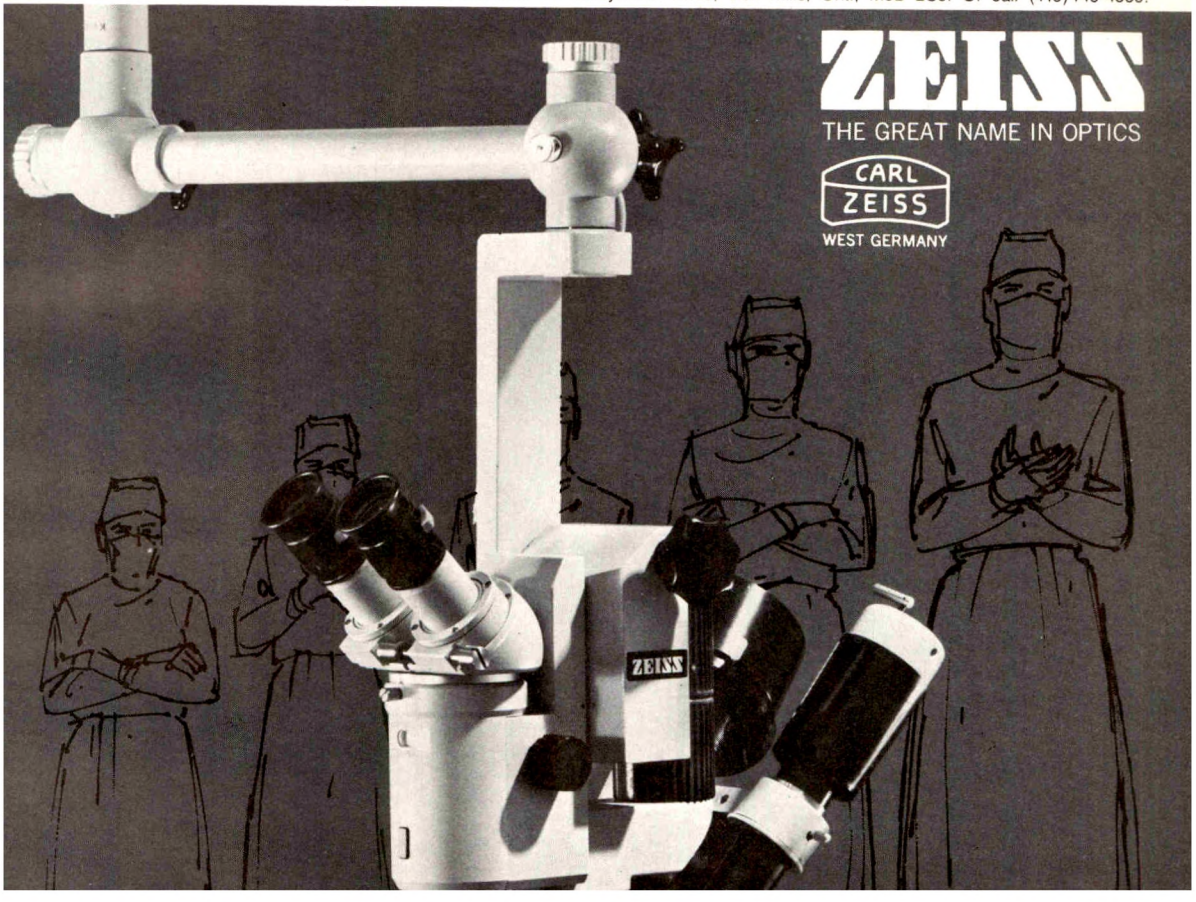
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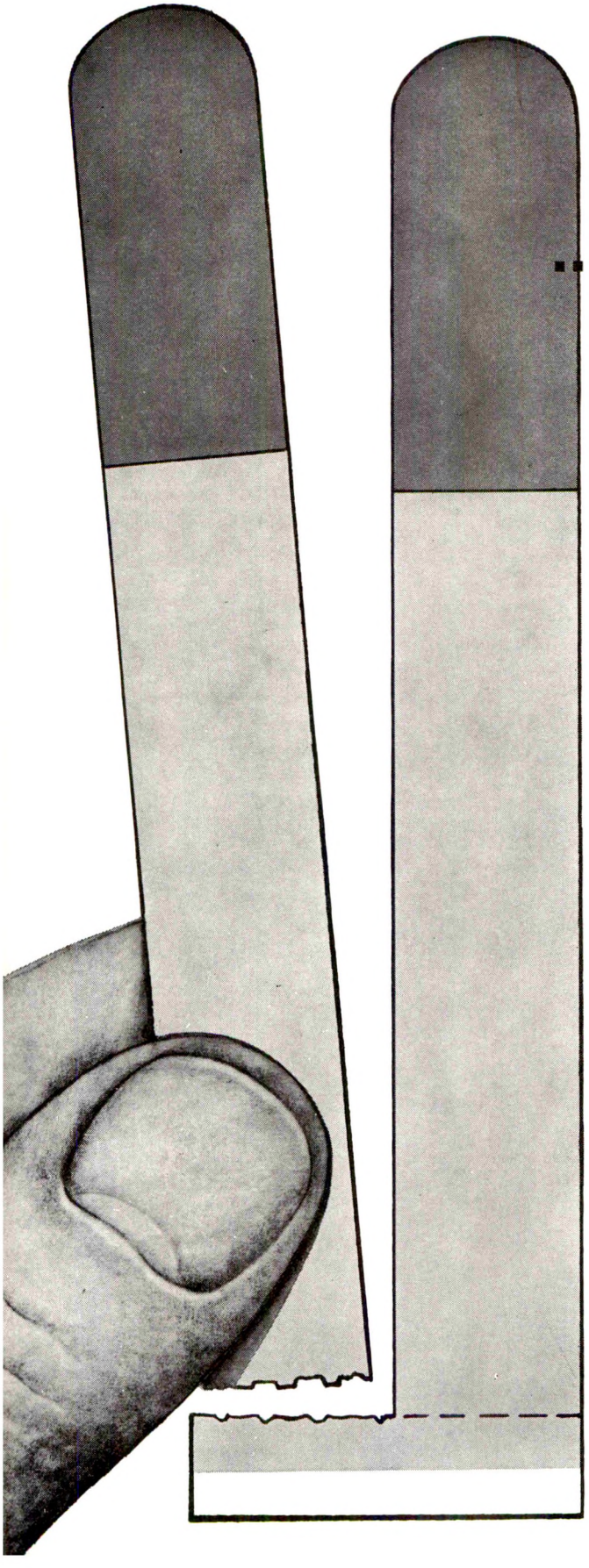
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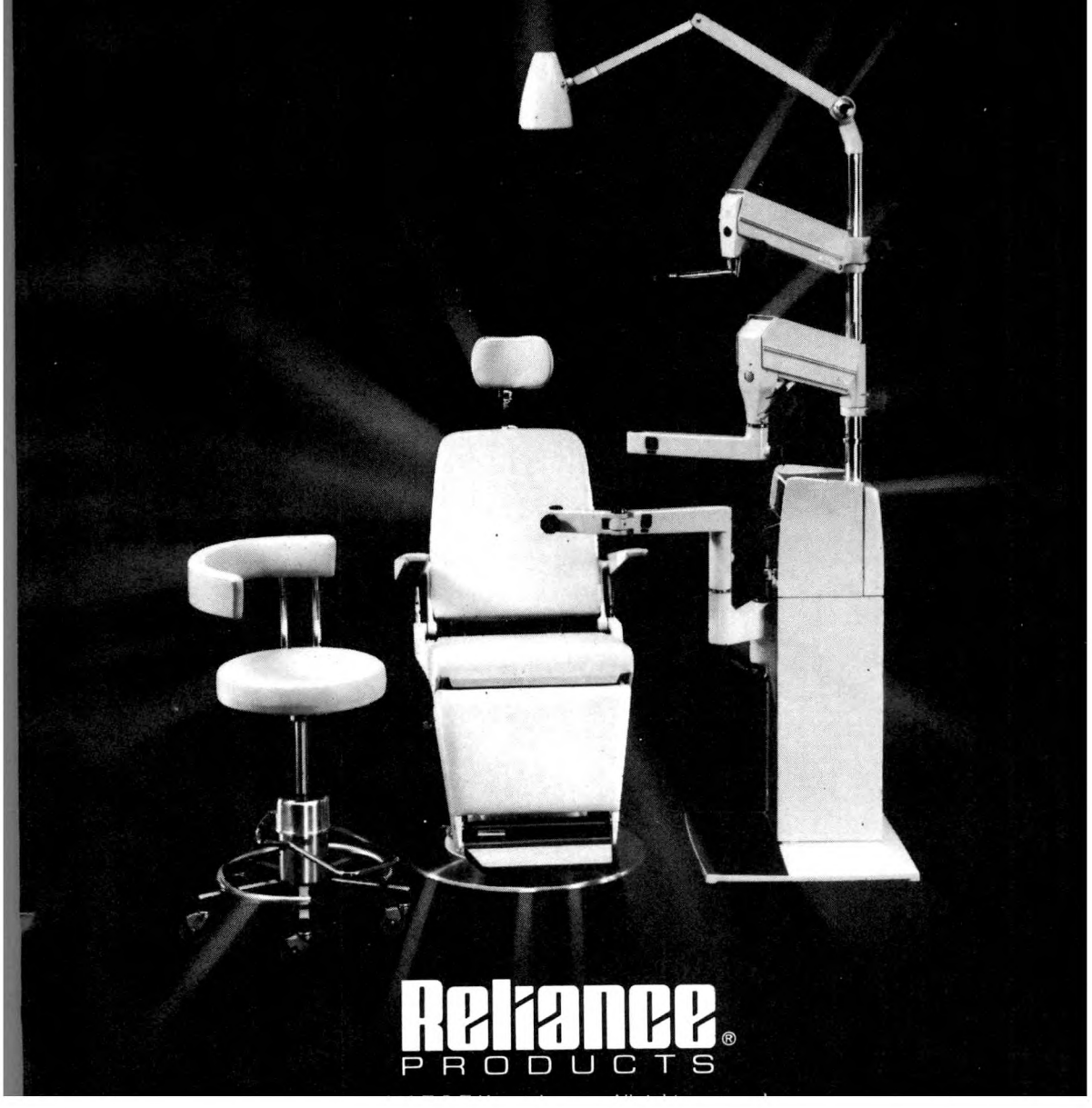
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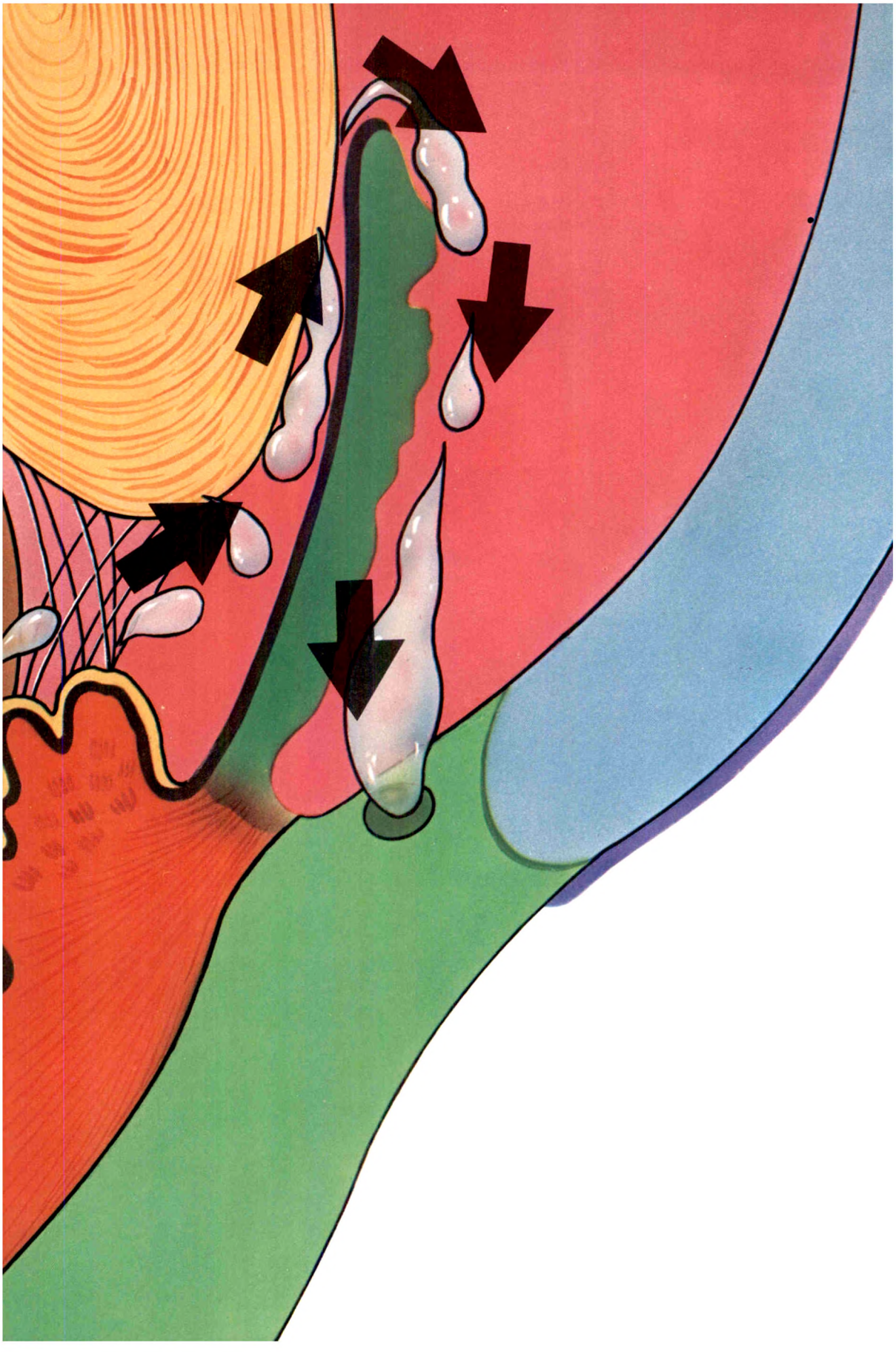
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OPHTHALMIC

Solution-Sterile
Ointment-Sterile

Each ml. or gram contains gentamicin sulfate equivalent to 3.0 mg. gentamicin.

DESCRIPTION Gentamicin sulfate is a water-soluble antibiotic of the aminoglycoside group active against a wide variety of pathogenic gram-negative and gram-positive bacteria.

GARAMYCIN **Ophthalmic Solution** is a sterile, aqueous solution buffered to approximately pH 7 for use in the eye. Each ml. contains gentamicin sulfate (equivalent to 3.0 mg. gentamicin), disodium phosphate, monosodium phosphate, sodium chloride, and benzalkonium chloride as a preservative.

GARAMYCIN **Ophthalmic Ointment** is a sterile ointment, each gram containing gentamicin sulfate (equivalent to 3.0 mg. gentamicin) in a bland base of white petrolatum, with methylparaben and propylparaben as preservatives.

ACTIONS The gram-positive bacteria against which gentamicin sulfate is active include coagulase-positive and coagulase-negative staphylococci, including certain strains that are resistant to penicillin. Group A beta-hemolytic and nonhemolytic streptococci, and *Diplococcus pneumoniae*. The gram-negative bacteria against which gentamicin sulfate is active include certain strains of *Pseudomonas aeruginosa*, indole-positive and indole-negative *Proteus* species, *Escherichia coli*, *Klebsiella pneumoniae* (Friedlander's bacillus), *Haemophilus influenzae* and *Haemophilus aegyptius* (Koch-Weeks bacillus), *Aerobacter aerogenes*, *Moraxella lacunata* (diplobacillus of Morax-Axenfeld), and *Neisseria* species including *Neisseria gonorrhoeae*. Although significant resistant organisms have not been isolated from patients treated with gentamicin at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.

INDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are indicated in the topical treatment of infections of the external eye and its adnexa caused by susceptible bacteria. Such infections embrace conjunctivitis, keratitis and keratoconjunctivitis, corneal ulcers, blepharitis and blepharoconjunctivitis, acute meibomianitis, and dacryocystitis.

CONTRAINDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are contraindicated in patients with known hypersensitivity to any of the components.

WARNINGS GARAMYCIN **Ophthalmic Solution** is not for injection. It should never be injected subconjunctivally, nor should it be directly introduced into the anterior chamber of the eye.

PRECAUTIONS Prolonged use of topical antibiotics may give rise to overgrowth of nonsusceptible organisms, such as fungi. Should this occur, or if irritation or hypersensitivity to any component of the drug develops, discontinue use of the preparation and institute appropriate therapy.

Ophthalmic ointments may retard corneal healing.

ADVERSE REACTIONS Transient irritation has been reported with the use of GARAMYCIN **Ophthalmic Solution.**

Occasional burning or stinging may occur with the use of GARAMYCIN **Ophthalmic Ointment.**

DOSAGE AND ADMINISTRATION GARAMYCIN **Ophthalmic Solution:** instill one or two drops into the affected eye every four hours. In severe infections, dosage may be increased to as much as two drops once every hour.

GARAMYCIN **Ophthalmic Ointment:** apply a small amount to the affected eye two to three times a day.

HOW SUPPLIED GARAMYCIN **Ophthalmic Solution—Sterile,** 5-ml. plastic dropper bottle, sterile, boxes of one and six. Store away from heat.

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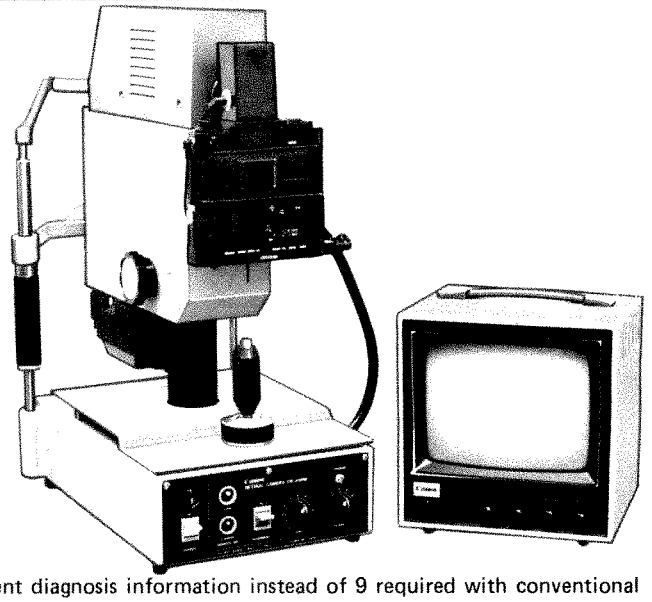
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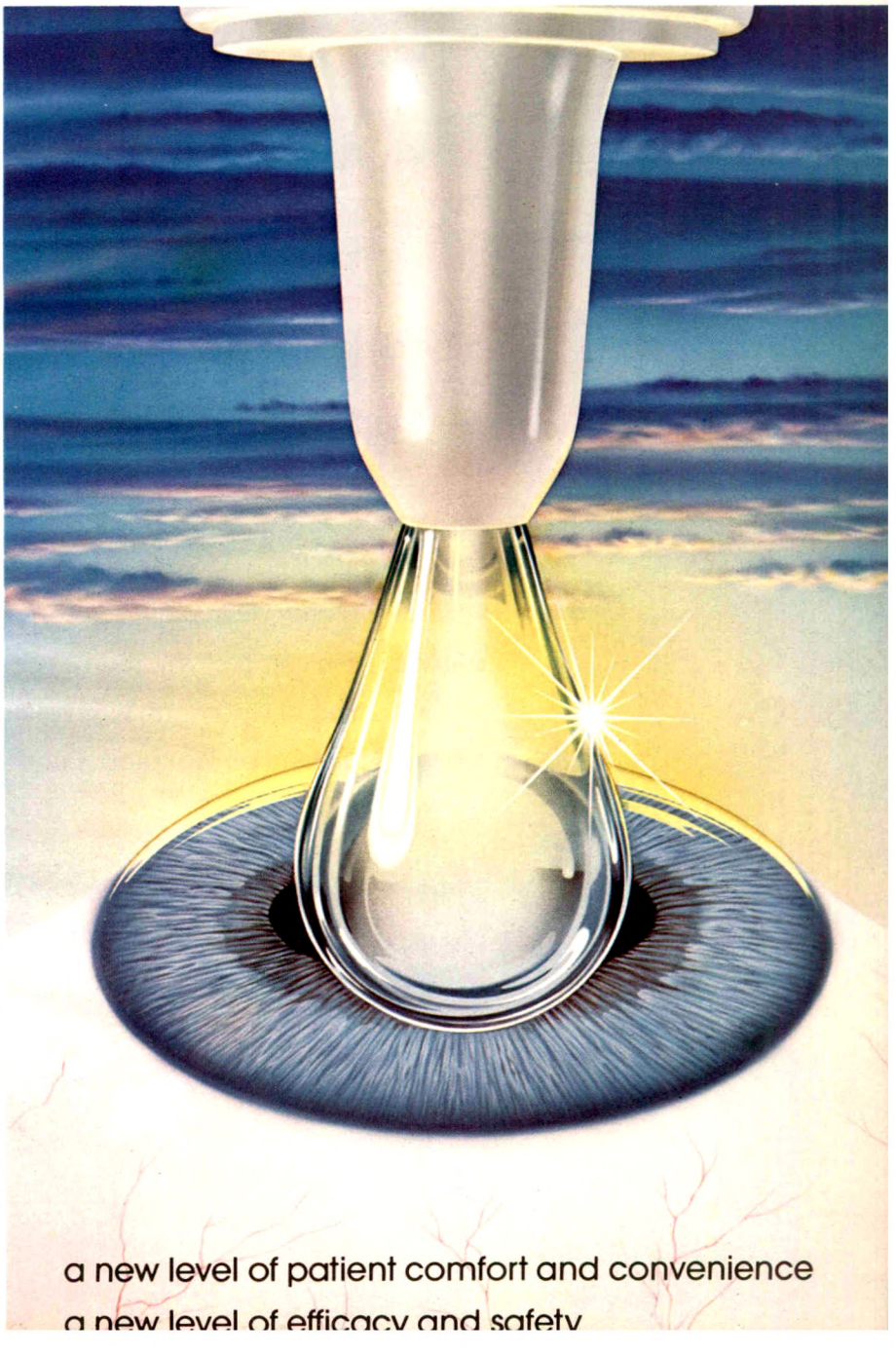
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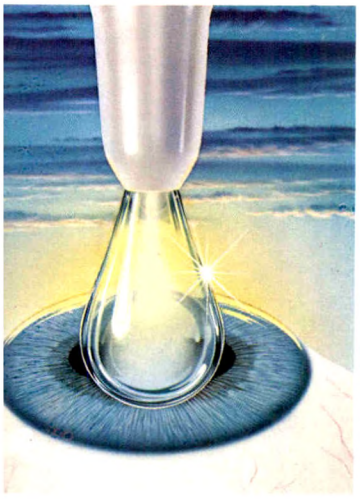
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a new level of efficacy and safety

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new Timoptic™

(TIMOLOL MALEATE | MSD) OPHTHALMIC SOLUTION

a beta-adrenergic blocking agent in ophthalmic solution...for reduction of elevated IOP in chronic open-angle glaucoma

significantly more effective than pilocarpine or epinephrine with fewer and less severe side effects*

- **little or no change in pupil size**
- **little or no blurring of vision**
- **no dimming of vision...no night blindness**
- **little or no effect on tear production**
- **little or no hyperemia**
- **simple "one-drop" b.i.d. dosage (may encourage long-term compliance)**

TIMOPTIC™ (Timolol Maleate, MSD) is contraindicated in patients who are hypersensitive to any component of this product.

Occasionally, mild ocular irritation has been reported.

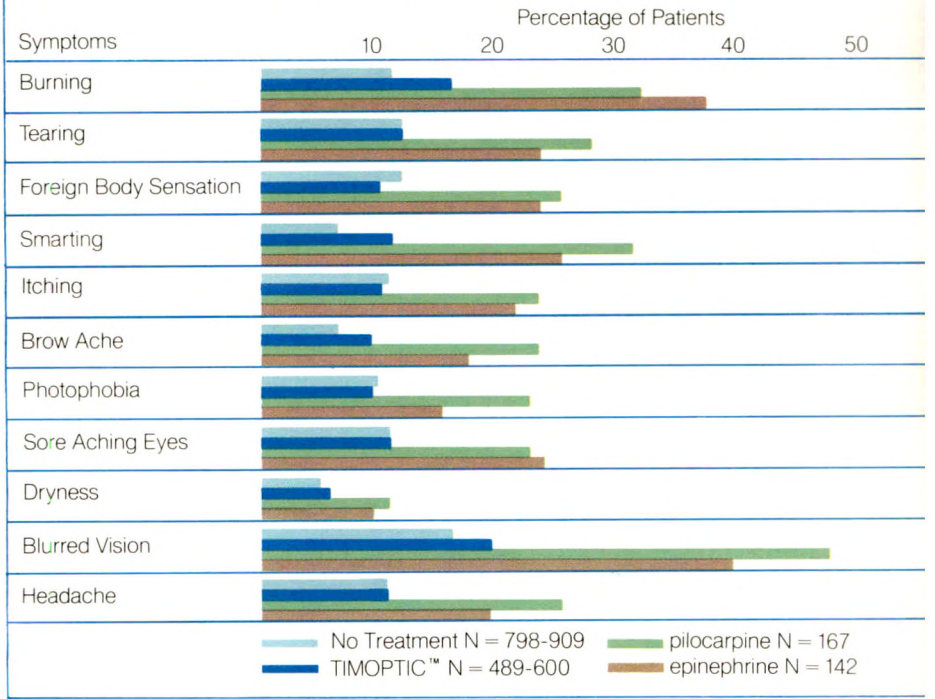
Sufficient clinical data have not been obtained to show safety or efficacy in narrow-angle or angle-closure glaucoma.

*Based on controlled multiclinic studies, evaluating over 1,000 patients. Data on file, Merck Sharp & Dohme. For published articles from the clinical studies on TIMOPTIC,™ please see last page of this advertisement.

a new level of patient comfort and convenience



In clinical studies—a much lower incidence of ocular discomfort than with pilocarpine or epinephrine



Adverse effects commonly caused by pilocarpine and epinephrine as reported in the literature—rarely encountered with TIMOPTIC™ (Timolol Maleate, MSD)

Drug-Induced Adverse Effects

pilocarpine	**TIMOPTIC™ (in clinical studies)**	**epinephrine**	**TIMOPTIC™ (in clinical studies)**
extreme miosis	none reported	conjunctival irritation	rare
spasm of accommodation	none reported	hyperemia	rare and mild
shallowing of the anterior chamber	none reported	macular edema in aphakic patients	none reported
night blindness and dimming of vision	none reported	pigment deposits on lid margins and conjunctiva	none reported
ciliary and conjunctival congestion	rare and mild		

With TIMOPTIC,™ slight reduction of the resting heart rate has been observed in some patients. Local hypersensitivity reactions have occurred rarely.

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new Timoptic™

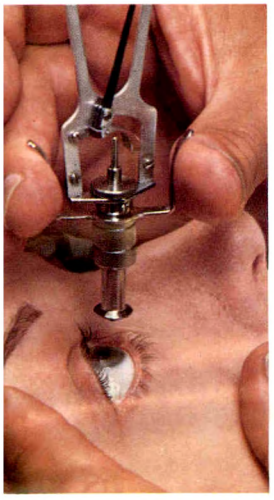
(TIMOLOL MALEATE | MSD) OPHTHALMIC SOLUTION

a beta-adrenergic blocking agent
in ophthalmic solution...for reduction of
elevated IOP in chronic open-angle glaucoma

- Fast onset of action (usually within ½ hour)
- Based on clinical studies of 638 patients maintained on therapy from 14 to 477 days:
  approximately 76% (485 of 638) of patients satisfactorily managed (IOP less than 22 mm Hg) on TIMOPTIC™ alone
  approximately 93% (593 of 638) of patients satisfactorily managed with TIMOPTIC™ alone or administered concomitantly with other antiglaucoma agents
- No evidence of diminished responsiveness reported in 102 patients treated for at least two years
- Absence of miosis may facilitate visualization of optic disc and evaluation of visual fields
- Usually well tolerated
- Produced fewer and less severe side effects than either pilocarpine or epinephrine

TIMOPTIC™ should be used with caution in patients with known contraindications to systemic use of beta-adrenergic receptor blocking agents. Patients who are already receiving a beta-adrenergic blocking agent orally should be observed for a potential additive effect.

a new level of efficacy and safety



In comparative clinical studies—significantly more effective than pilocarpine or epinephrine

In multiclinic studies, TIMOPTIC™ (Timolol Maleate, MSD) reduced IOP in proportionately more patients





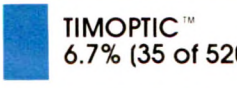




% of patients with IOP reduced to less than 22 mm Hg ($p < 0.01$)

Data are derived from the final visit (week 17) in the multiclinic pilocarpine and epinephrine comparative studies. These include patients who withdrew due to ineffective response or an adverse clinical experience.

In all clinical studies, therapy with TIMOPTIC™ resulted in fewer dropouts* than with pilocarpine or epinephrine





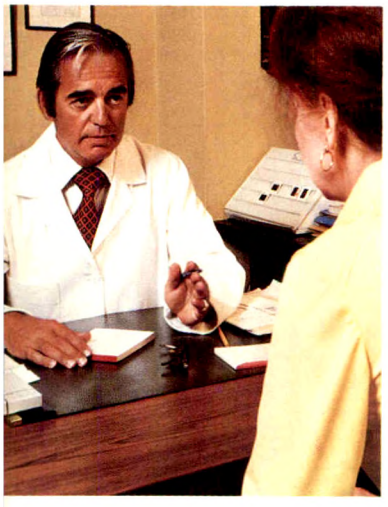


Data include patients participating in clinical studies lasting 14 to 477 days.

*Dropouts are defined as patients whose IOP could not be reduced to levels below 22 mm Hg, or those who withdrew because of an adverse clinical experience.

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For a brief summary of Prescribing Information, please see last page of this advertisement.



new Timoptic™

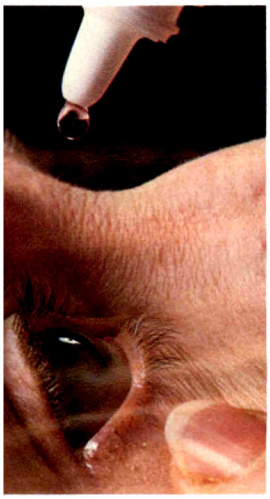
(TIMOLOL MALEATE | MSD) OPHTHALMIC SOLUTION

significantly broadens the medical options in antiglaucoma therapy

- **Permits prolonged maintenance therapy—no evidence of tolerance reported** In a clinical study of 102 patients treated for at least two years, there was no evidence of diminished responsiveness to TIMOPTIC™.
- **Compatible with other agents** Concomitant therapy with pilocarpine and other miotics, and/or epinephrine, and/or systemically administered carbonic anhydrase inhibitors, such as acetazolamide, can be instituted for the patient who needs reduction of IOP greater than provided by one drop of 0.5% TIMOPTIC™ twice a day. Dosages above one drop of 0.5% TIMOPTIC™ twice a day generally have not been shown to produce further reduction in intraocular pressure.
- **Helpful in the medical management of a broader range of patients** In some patients who respond inadequately to maximum available drug therapy, the addition of TIMOPTIC™ may result in satisfactory management of intraocular pressure, thus possibly postponing the need for surgery.
- **Often effective in patients previously difficult to manage**...such as working patients incapacitated by accommodative spasm produced by miotics, older patients with cataracts whose vision is impaired with miotics, patients with heavily pigmented irides whose response to pilocarpine is diminished, and aphakic patients who may develop macular edema from epinephrine.

Since clinical studies in children have not been done, TIMOPTIC™ is not recommended for use in children at this time. TIMOPTIC™ has not been studied in human pregnancy. The use of TIMOPTIC™ in pregnant women requires that the anticipated benefits be weighed against the possible hazards.

a beta-adrenergic blocking agent in ophthalmic solution...for reduction of elevated IOP in chronic open-angle glaucoma



Dosage Guidelines:

How to transfer from current therapy to TIMOPTIC™ (Timolol Maleate, MSD):

1 On the first day: continue with the agent(s) already being used and add one drop 0.25% TIMOPTIC™ in each eye b.i.d.

2 On the second day: discontinue the previously used agent(s) and continue with TIMOPTIC™ in each eye b.i.d.

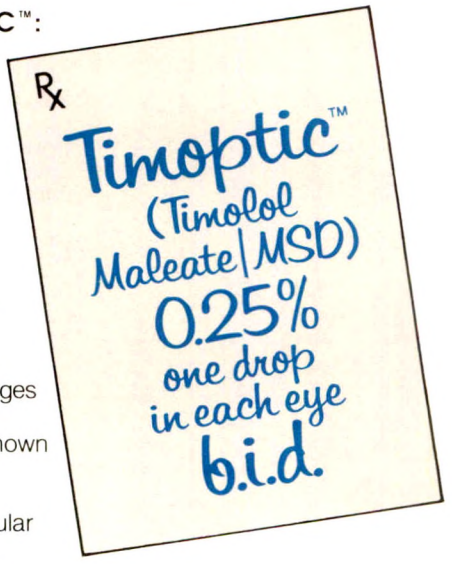
How to add TIMOPTIC™ to other agents:

1 Administer one drop 0.25% TIMOPTIC™ in each eye b.i.d....while continuing with the agent(s) already being used.

2 If a higher dosage of TIMOPTIC™ is required, substitute one drop 0.5% TIMOPTIC™ in each eye b.i.d....while continuing with the agent(s) already being used.

How to start patients on TIMOPTIC™:

Usual starting dosage:
one drop 0.25% TIMOPTIC™
in each eye twice a day.



If clinical response is not adequate:

Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC™ twice a day in each eye. If the intraocular pressure is maintained at satisfactory levels, the dosage schedules may be changed to one drop once a day in each eye. Dosages above one drop of 0.5% TIMOPTIC™ twice a day generally have not been shown to produce further reduction in IOP.

Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

In patients with a history of severe cardiac disease, pulse rates should be checked.

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For a brief summary of Prescribing Information, please see following page.

for many patients—a significant advance for the reduction of elevated IOP

- in chronic open-angle glaucoma
- in ocular hypertension
- in aphakic glaucoma
- in some patients with secondary glaucoma

new Timoptic™

(TIMOLOL MALEATE) MSD OPHTHALMIC SOLUTION



BIBLIOGRAPHY

Published Articles from Clinical Studies on TIMOPTIC™

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5. Radius, R., Diamond, G., Pollack, I., and Langham, M.: Timolol: A new drug for manageme of chronic simple glaucoma, Arch. Ophthalmol. *96(6)*:1003-1008, June 1978.
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10. Zimmerman, T. and Kaufman, H.: Timolol: a new drug for the treatment of glaucoma?, in *Symposium on Ocular Therapy*, ed. I. H. Leopold, vol. 10, New York, John Wiley & Sons, 1977, pp. 69-76.
11. Zimmerman, T. and Kaufman, H.: Timolol: Dose response and duration of action, Arch. Ophthalmol. *95(4)*:605-607, April 1977.

CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients who are hypersensitive to any component of this product.

PRECAUTIONS: Should be used with caution in patients with known contraindications to systemic use of beta-adrenergic receptor blocking agents. These include bronchial asthma; sinus bradycardia and greater than first-degree block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure; concomitant use with adrenergic-augmenting psychotropic drugs. In patients with a history of severe cardiac disease, pulse rates should be checked. Patients who are already receiving a beta-adrenergic blocking agent orally and who are given TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blocka

Sufficient clinical data have not been obtained to show safety or efficacy in narrow-angle or angle-closure glaucoma.

Pregnancy: TIMOPTIC has not been studied in human pregnancy. The use of TIMOPTIC in pregnant women requires that the anticipated benefit be weighed against possible hazards.

Use in Children: Since clinical studies in children have not been done, TIMOPTIC is not recommended for use in children at this time.

ADVERSE REACTIONS: Occasionally, signs and symptoms of mild ocular irritation have been reported. Slight reduction of the resting heart rate (mean reduction 2.9 beats/minute, standard deviation 10.2) has been observed in some patients. Local hypersensitivity reactions have occurred rarely.

Note: TIMOPTIC has been used in patients with glaucoma wearing conventional (PMMA) hard contact lenses, and has generally been well tolerated. TIMOPTIC has not been studied in patients wearing lenses made with materials other than PMMA.

HOW SUPPLIED:

TIMOPTIC Ophthalmic Solution, 0.25%
TIMOPTIC Ophthalmic Solution, 0.5%

Both are available in 5-ml plastic OCUMETER® Ophthalmic Dispenser with a controlled drop tip

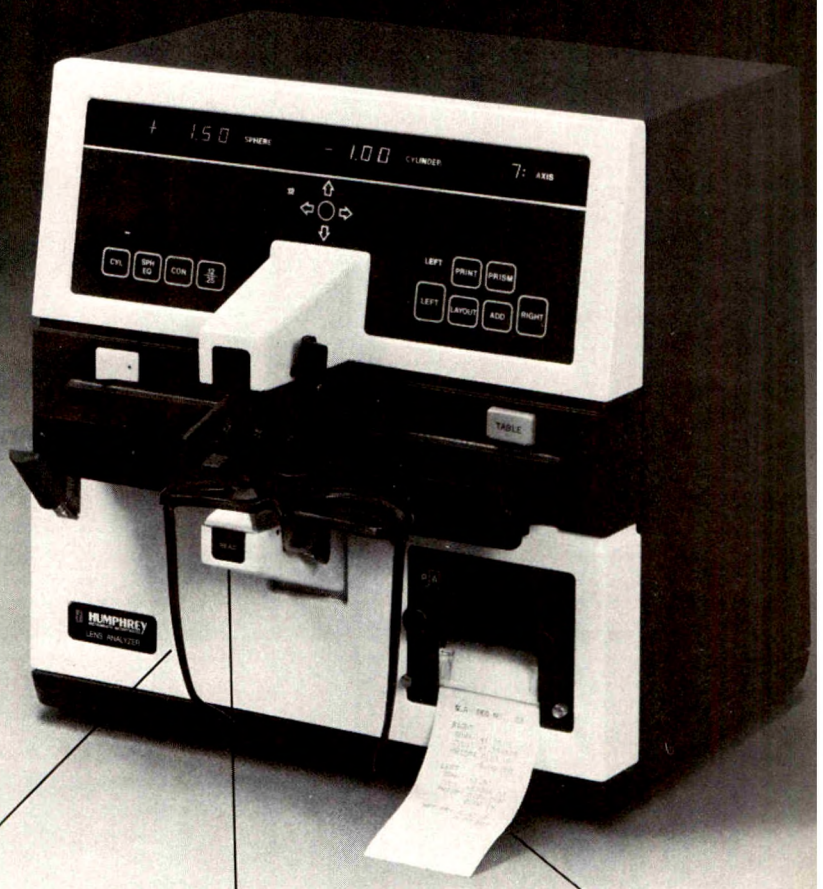
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For more detailed information, consult your MSD Representative or see full Prescribing Informa

Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486.

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Step Up To Automatic Lens Measurement For Less Than $4700



The Humphrey Lens Analyzer is several steps above other lensmeters. It is fast and very accurate. Completely objective measurement makes operator error virtually impossible.

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You easily check glasses as a pair, single lenses and contact lenses.

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R_x appears on digital readout and on (optional) hard copy printer.

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Sphere Range	±30 D (0.12D & 0.25D increments)
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Cylinder Axis	0-180° (1° increments)
Vertical Prism	±15 (.25 increments)
Lateral Prism	±15 (.25 increments)
Size	13″ wide x 12″ deep x 14″ high

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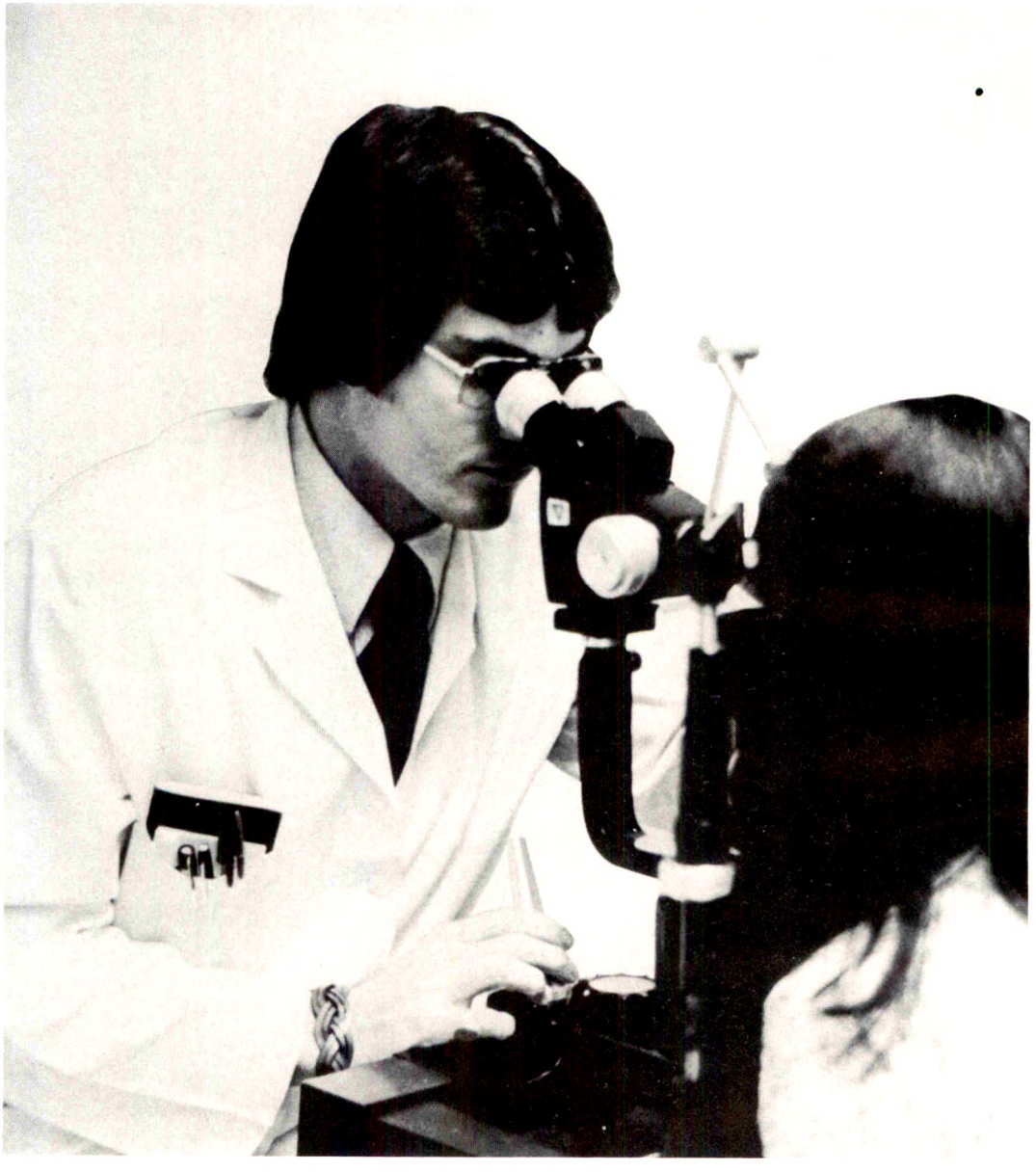
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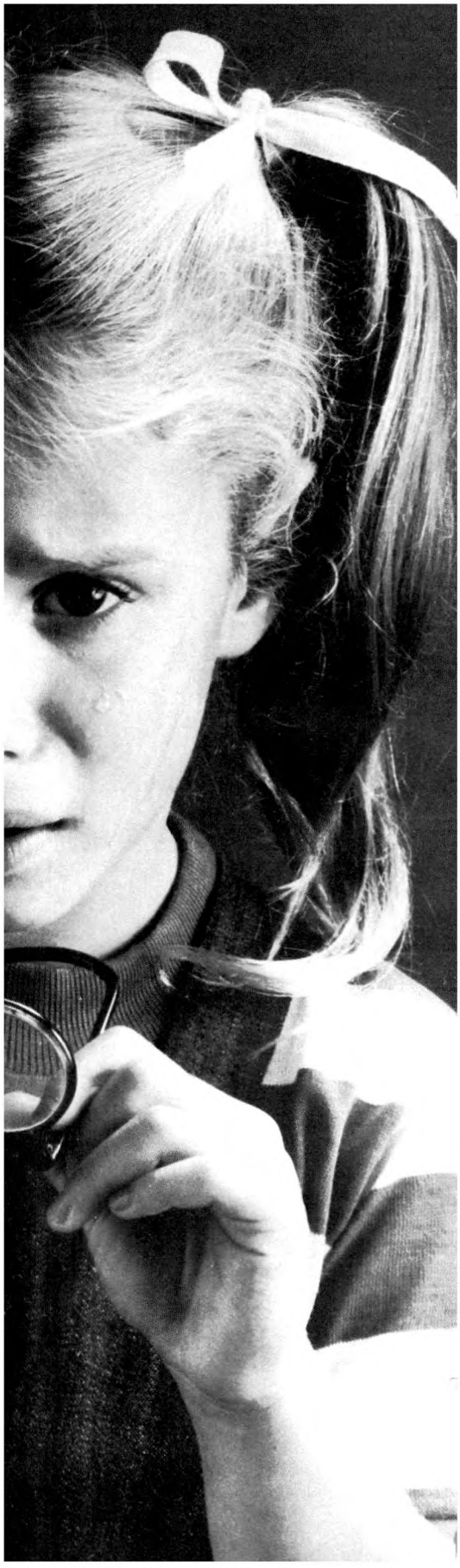
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Phospholine Iodide®

ECHOTHIOPHATE IODIDE FOR OPHTHALMIC SOLUTION)

for accommodative esotropia

The emotional impact of accommodative esotropia on a young child need not necessarily be followed by the trauma of surgery or the inconvenience and problems associated with wearing and caring for prescription lenses. The agent frequently used in the diagnosis of the condition is the same agent that can be used to correct the accommodative factor without inconvenience to the young patient.

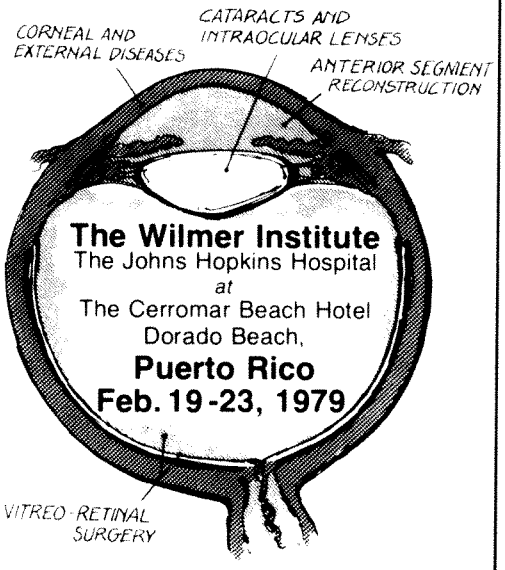
In diagnosis... One drop of PHOSPHOLINE IODIDE 0.125% instilled daily in each eye prior to retiring, for two or three weeks, will help to determine if there is an accommodative basis for the esotropia.

In treatment... If there is a significant accommodative factor present, the continued use of PHOSPHOLINE IODIDE alone is often sufficient to correct the problem, as long as the drug is well tolerated. PHOSPHOLINE IODIDE acts by altering the accommodative convergence/accommodation relationship in a favorable way, so that near vision is obtained with less accommodative effort and fusion can frequently be reestablished.
If corrective lenses are necessary, PHOSPHOLINE IODIDE may permit the use of single vision lenses instead of bifocals.
If surgery is necessary, postoperative use of PHOSPHOLINE IODIDE may help correct a residual deviation.

BRIEF SUMMARY
(For full prescribing information, see package circular.)
PHOSPHOLINE IODIDE®
(ECHOTHIOPHATE IODIDE FOR OPHTHALMIC SOLUTION)
PHOSPHOLINE IODIDE is a long-acting cholinesterase inhibitor for topical use.
Indications: Glaucoma – Chronic open-angle glaucoma. Subacute or chronic angle-closure glaucoma after iridectomy or where surgery is refused or contraindicated. Certain non-uveitic secondary types of glaucoma, especially glaucoma following cataract surgery.
Accommodative esotropia – Concomitant esotropias with a significant accommodative component.
Contraindications: 1. Active uveal inflammation.
2. Most cases of angle-closure glaucoma, due to the possibility of increasing angle block.
3. Hypersensitivity to the active or inactive ingredients.
Warnings: 1. *Use in Pregnancy.* Safe use of anticholinesterase medications during pregnancy has not been established, nor has the absence of adverse effects on the fetus or on the respiration of the neonate.
2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patients receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.
3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same time undergoing treatment with systemic anticholinesterase medications for myasthenia gravis, because of possible adverse additive effects.
Precautions: 1. Gonioscopy is recommended prior to initiation of therapy.
2. Where there is a quiescent uveitis or a history of this condition, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.
3. While systemic effects are infrequent, proper use of the drug requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into the nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.
4. Temporary discontinuance of medication is necessary if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregularities occur.
5. Patients receiving PHOSPHOLINE IODIDE who are exposed to carbamate or organophosphate type insecticides and pesticides (professional gardeners, farmers, workers in plants manufacturing or formulating such products, etc.) should be warned of the additive systemic effects possible from absorption of the pesticide through the respiratory tract or skin. During periods of exposure to such pesticides, the wearing of respiratory masks, and frequent washing and clothing changes may be advisable.
6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects.
7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.
8. PHOSPHOLINE IODIDE (echothiophate iodide) should be used with great caution, if at all, where there is a prior history of retinal detachment.
Adverse Reactions: 1. Although the relationship, if any, of retinal detachment to the administration of PHOSPHOLINE IODIDE has not been established, retinal detachment has been reported in a few cases during the use of PHOSPHOLINE IODIDE in adult patients without a previous history of this disorder.
2. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.
3. Activation of latent iritis or uveitis may occur.
4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.
5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.
6. Lens opacities occurring in patients under treatment for glaucoma with PHOSPHOLINE IODIDE have been reported and similar changes have been produced experimentally in normal monkeys. Routine examinations should accompany clinical use of the drug.
7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.
Overdosage: Antidotes are atropine, 2 mg parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg per kg intravenously; artificial respiration should be given if necessary.
How Supplied: Four potencies are available: 1.5 mg package for dispensing 0.03% solution; 3.0 mg package for 0.06% solution; 6.25 mg package for 0.125% solution; 12.5 mg package for 0.25% solution. Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chorobutanol (chloral derivative), mannitol, boric acid and exsiccated sodium phosphate.

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(Precedes XII Pan Am Congress, Miami, Feb. 25)

Sodium SULAMYD®
brand of sodium sulfacetamide, U.S.P.
Ophthalmic Solution 30%, Solution 10%, Ointment 10% – Sterile
INDICATIONS Sodium SULAMYD is indicated for the treatment of conjunctivitis, corneal ulcer, and other superficial ocular infections due to susceptible microorganisms, and as adjunctive treatment in systemic sulfonamide therapy of trachoma.
CONTRAINDICATIONS Hypersensitivity to sulfonamide preparations contraindicates the use of Sodium SULAMYD.
PRECAUTIONS The solutions are incompatible with silver preparations. Ophthalmic ointments may retard corneal healing. Non-susceptible organisms, including fungi, may proliferate with the use of these preparations. Sulfonamides are inactivated by the para-aminobenzoic acid present in purulent exudates. Sulfonamide sensitivity reactions may occur.
June 1972 9838358

METIMYD®
brand of prednisolone acetate, U.S.P., and sulfacetamide sodium, U.S.P.
Ophthalmic Suspension and Ointment – Sterile. Each ml or Gm contains 5 mg. prednisolone acetate and 100 mg. sulfacetamide sodium.

INDICATIONS – *Suspension* Based on a review of this drug by the National Academy of Sciences – National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: for the treatment of the following inflammatory and allergic conditions affecting the eyelids and anterior segment of the eye: EYELIDS: allergic blepharitis, blepharitis associated with seborrheic dermatitis and other nonpurulent forms of conjunctivitis including those associated with hay fever, and conjunctivitis due to physical agents such as foreign bodies, chemicals (acids, alkalies) and other irritants. CORNEA, SCLERA, IRIS, AND UVEA: interstitial, postoperative, and sclerosing keratitis; chemical and thermal burns of the cornea; corneal ulcer; herpes zoster ophthalmicus; phlyctenular keratoconjunctivitis; corneal neovascularization; scleritis; episcleritis; acute, chronic, and traumatic iridocyclitis.
Final classification of the less-than-effective indications requires further investigation.

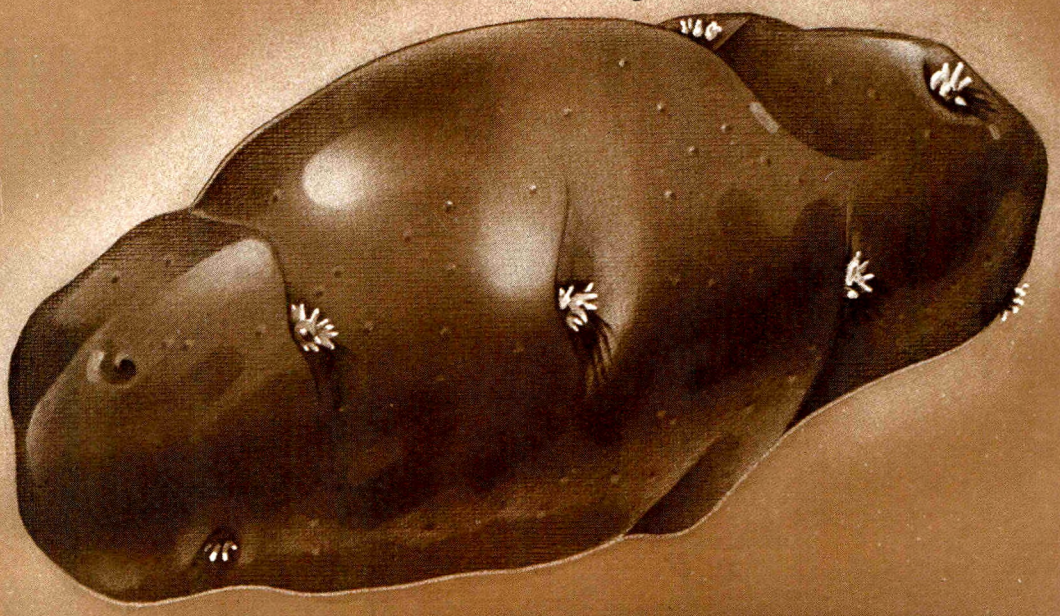
Ointment METIMYD is indicated in the following inflammatory and allergic conditions affecting the eyelids and anterior segment of the eye:
Eyelids: allergic blepharitis; blepharitis associated with seborrheic dermatitis; other nonpurulent types of blepharitis.
Conjunctiva: allergic conjunctivitis (e.g. vernal); phlyctenular; and other nonpurulent forms of conjunctivitis including those associated with hay fever; conjunctivitis due to physical agents such as foreign bodies; chemicals (acids, alkalies); and other irritants.
Cornea, Sclera, Iris, Uvea: interstitial, postoperative, and sclerosing keratitis; chemical and thermal burns of the cornea; corneal ulcer; herpes zoster ophthalmicus; phlyctenular keratoconjunctivitis; corneal neovascularization; scleritis; episcleritis; acute, chronic, and traumatic iridocyclitis.
In deep-seated infections, such as endophthalmitis, panophthalmitis, and orbital cellulitis, or when systemic infection threatens, specific oral (antibiotic, sulfonamide) therapy should be employed. Local treatment may be used as adjunctive therapy.
CONTRAINDICATIONS The contraindications for METIMYD are the same as those for other corticosteroid-sulfonamide preparations. Topical ophthalmic corticosteroid preparations and combinations are contraindicated in: early acute herpes simplex and the early acute stages of most other viral diseases of the cornea and conjunctiva; active tuberculosis of the anterior segment of the eye; fungal disease of the cornea, conjunctiva and lids; acute purulent untreated infections of the eye which, like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid; individuals with known sensitivity to any of the ingredients.
PRECAUTIONS Extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. In prolonged therapy, it is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to have occurred with the use of topical steroids. As with any antibacterial preparation, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate measures should be instituted. Sensitivity reactions may occur in certain individuals. If signs of sensitivity develop, discontinue use.
The protracted use of topical corticosteroids in the eye reportedly has been rarely associated with the development of posterior subcapsular cataracts.
January 1973, July 1973 9835356, 10106524

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Schering Ophthalmic Products aren't for all eyes...



But, when your patients have eye disorders...*

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sulfonamide antibacterial for superficial ocular infections†

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OPHTHALMIC OINTMENT 10%-STERILE

anti-inflammatory‡/antibacterial in external eye infections†‡

METIMYD®

brand of prednisolone acetate, USP and sulfacetamide sodium, USP
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Schering Ophthalmics
Specific products for specific needs

†due to susceptible pathogens
‡This drug has been evaluated as "possibly effective" for this indication.

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Before prescribing, please see full product information, brief summaries of which appear on opposite page.



Fabricated from a highly purified, medical grade of cellulose acetate butyrate, The Meso Lens offers significant advantages over both hydrogel and PMMA lenses.

The Meso Lens:

- Provides a new experience in wearing comfort without sacrificing durability or crisp visual acuity.
- Demonstrates enhanced wettability (approaching the angle produced by the normal hydrophilic cornea), improved tear exchange, and a heat-transfer coefficient considerably greater than PMMA.
- Can be fit using keratometry or conventional trial set procedures (including fluorescein patterns) for the visual correction of *astigmatism, myopia, hyperopia* and *aphakia.*

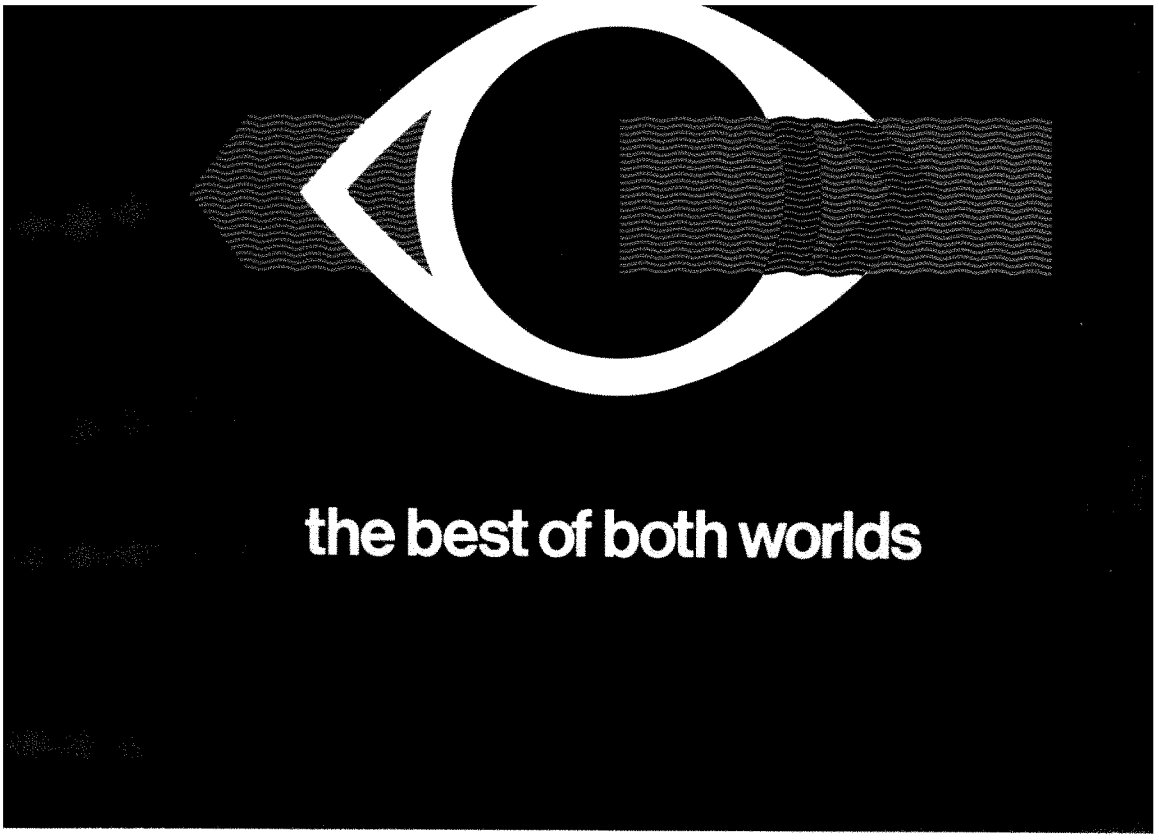
An extensive series of clinical trials on 825 wearers has demonstrated the stability, safety, and efficacy of The Meso Lens. Based on a statistical analysis of the data, it is reasonable to expect the following:

1. Rapid Adaptation/Increased Wearing Time Corneal integrity is rarely impaired. The average adaptation period is comparable to that observed with soft lenses: 8 hours wearing time within 7 days; 12 to 15 hours in less than two weeks – with the potential for interrupted-wear.

2. Reduced Signs of Overwearing The investigators cited longer wearing periods. In 1,796 slit-lamp observations, a 1.2% incidence of corneal edema and spectacle blur was reported.

3. Flexibility and Ease of Fitting Fitting The Meso Lens 0.25 diopter steeper or flatter, or with diameter differences of 0.1 or 0.2 mm, will not cause any significant change in comfort or acuity.

Parameters which affect tear exchange, such as apical clearance and intermediate bearing, are not critical. This increased latitude, particularly important in fitting astigmatic corneas, can be attributed to



the characteristics of the cabufocon material as well as to the unique optical design of The Meso Lens.

4. Simplified Lens Care A three-solution maintenance system utilizing Preflex®, Normol®, and Flexsol® for cleaning, rinsing and disinfecting, is recommended for The Meso Lens.

Virtually no solution-related problems, such as discoloration, binding of preservatives or drug sensitivity, have been reported with The Meso Lens.

NOTE: Thermal disinfection or the use of hard lens care products is contraindicated.

5. Crisp Visual Acuity In a group of 773 eyes fit with The Meso Lens 97.3% tested 20/25 – *or better than the best possible vision attained with spectacles in the same series.*

Danker and Wohlk's exclusive molding process is utilized in the precision manufacture of The Meso Lens. The result: Uniformly good edges, high reproducibility and a smooth finish, which will resist accumulation of surface deposits.

The Meso Lens is available in a wide range of base curves and diameters, 6.0 to 9.0 mm and 6.0 to 12 mm respectively. The Meso Lens deserves a trial with new patients and wearers presenting problems with PMMA or HEMA lenses.

See package insert and professional fitting guide for complete information.
For further details, call toll-free 800-645-1388 or write:

DANKER & WOHLK, INC.
635 Nassau Road, Uniondale, N.Y. 11553

the MESO® (cabufocon) lens

Description: The MESO® Contact Lens is a non-absorbent contact lens composed of the polymer, cellulose acetate butyrate.

It is manufactured in a range of base curves (6.0-9.0 mm) and diameters (6.0-12.5 mm) to permit custom fitting of the cornea.

Action: The MESO® (cabufocon) Contact Lens, when placed on the human cornea, acts as a refracting medium to correct myopia, hyperopia, astigmatism and aphakia.

Indication: The MESO® (cabufocon) Contact Lens is indicated for the correction of visual acuity in non-diseased eyes and aphakia.

Contra-indication: MESO® (cabufocon) Contact Lenses are contraindicated in the presence of any of the following conditions:

1. Active conjunctivitis;
2. Active or chronic trachoma infection;
3. Active herpes infection;
4. Any condition which has led to extensive corneal neovascularization;
5. Corneal hypoesthesia except that resulting from aphakia;
6. Any situation in which the wearer is unable to maintain good lens care regimen.

Warnings: The MESO® (cabufocon) Contact Lens must be stored only in Flexsol® Solution. No other storage solution is recommended. Patients must adhere to the recommended daily care regimen. Failure to do so may result in ocular infection.

If the lens becomes more uncomfortable to the wearer than when first placed on the eye, the lens should be removed, checked for dirt or scratches, and cleaned. If this condition persists or if the eye becomes red or painful, the lens should be removed immediately. If symptoms persist, your eye-care practitioner should be consulted.

The MESO® (cabufocon) Contact Lens should be removed before sleeping or swimming and should not be worn in the presence of noxious fumes or vapors. If unusual visual blurring occurs, the lens should not be worn until the condition subsides.

Precautions:
Lens Care — Storage: When the MESO® (cabufocon) Contact Lens is removed from the eye, it should be stored only in Flexsol® Sterile Soaking Solution after cleaning with Preflex®. The lens should be completely covered with the Flexsol® solution. Fill the lens case receptacle till just below the rim.

Before placing the MESO® (cabufocon) lens on the eye, rinse the lens with Normol® Solution. Discard the Flexsol® in the case, rinse the case with Normol® and dry the case. Refill with fresh Flexsol® solution each time the lens is stored.

The MESO® (cabufocon) lens, unlike the hydrophilic soft lens, does not dry out or become brittle if exposed to air. If the lens does become dry, it should be soaked in Flexsol® for a minimum of four hours before reinsertion in the eye.

Fluorescein may be used with the lens.

Lens Cleaning: Ordinary mucous and oily deposits are removed with daily cleaning of the lens with Preflex® as described in your Patient Booklet.

Adverse Reactions: As with any contact lens, corneal edema and corneal abrasions may occur if the lens is not properly fit, or if the wearing time is excessive.

Dose and Administration: A gradual build up of wearing time is recommended. A recommended schedule is as follows:

A. On the day of the initial fitting, two to four hours continuous wear.
B. Increase one hour each day for one week until eight continuous hours have been achieved.
C. If checkup is normal, wearing time is again increased by one hour a day until full time (12 or more hours) is achieved.

Wearing schedule should be determined by the eye care practitioner.

Studies have not been performed to support safety for extended wear of this lens.

How Supplied: Each lens is supplied in a sealed sterile packet. The packet is identified with the dioptric power, base curve, center thickness and manufacturer's lens number.

When the lens is removed from the packet, it should be stored in Flexsol® Solution for at least four hours prior to dispensing to ensure maximum patient comfort.

CAUTION: Federal law prohibits dispensing without prescription.

DANKER & WOHLK, INC.
635 Nassau Road, Uniondale, N.Y. 11533



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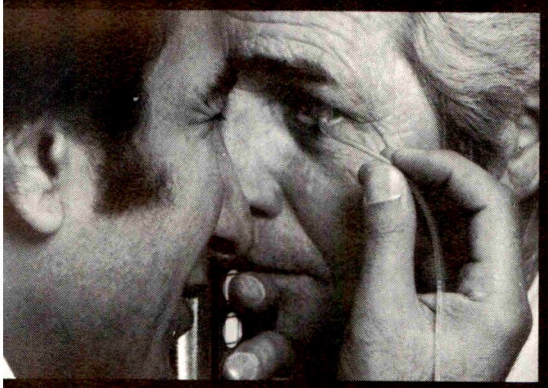
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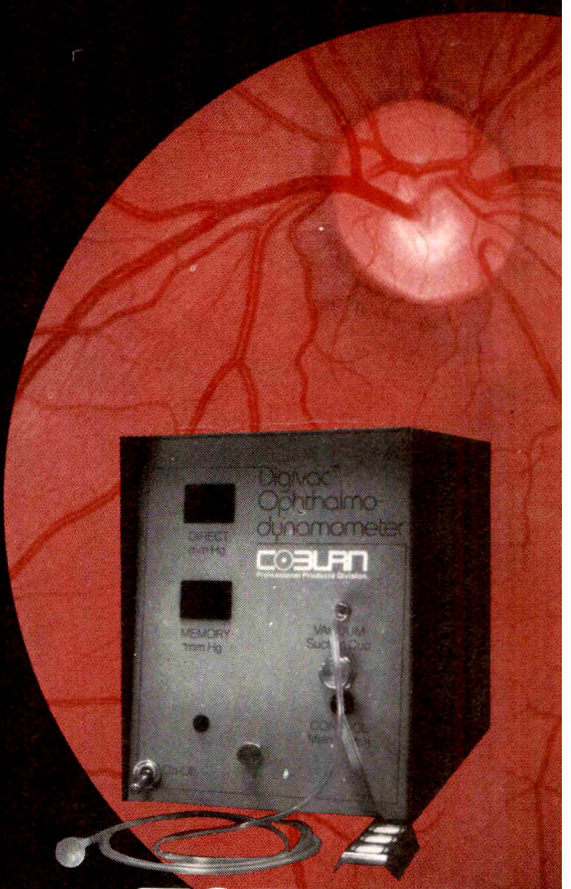
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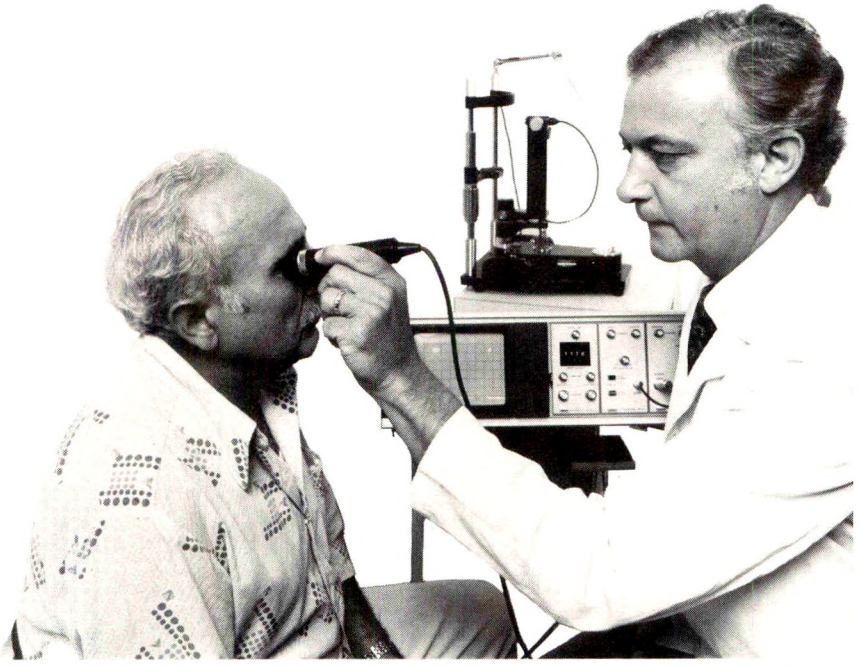
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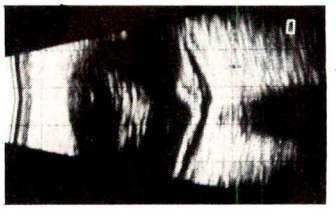
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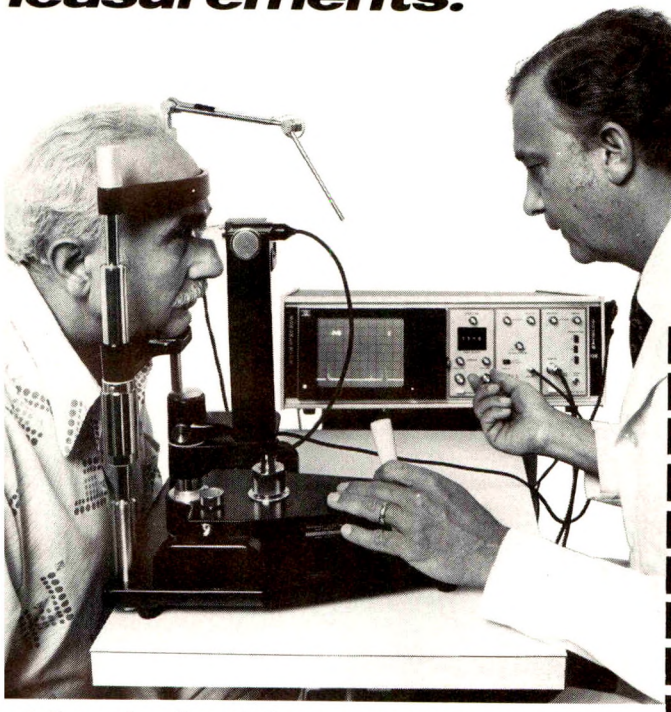
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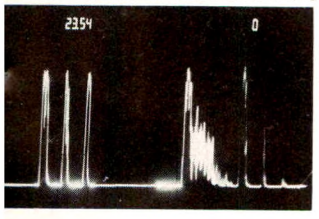
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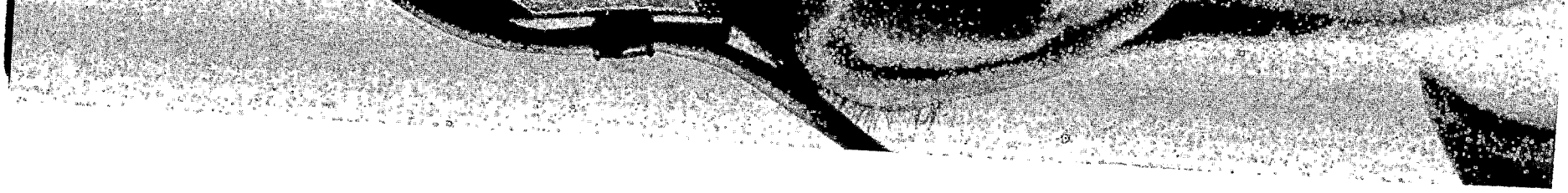
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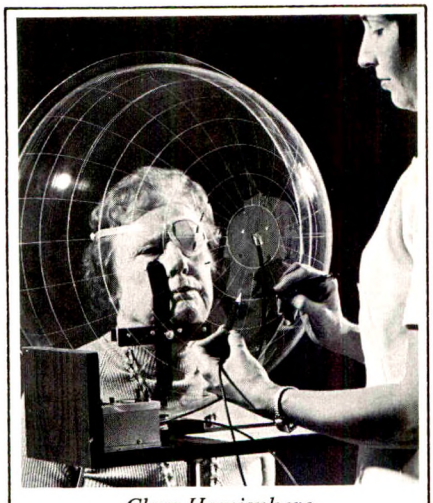
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The most exacting determination of scotomas can be done in both the central and peripheral fields because the target is seen directly without a blur, and can be moved up or down, in or out a milimeter or two at a time. No other method gives as definite "see" or "not seen" when outlining the normal blind spot.

In less time than it takes to make a referral to a perimetrist, one can do a very accurate confrontation test, and if normal as so often happens, all that needs to be recorded is "NORMAL". If you or your assistant find a defect, a record is easily made by marking the hemisphere with red and black grease pencils, then transferring it to special charts (furnished) that are printed on both sides. The CONFRONTATION side is placed face up over a carbon paper also face up. When scotomas are recorded the reverse, or PATIENT side, can be viewed which is the more common method.

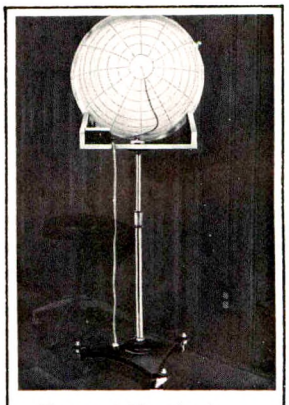
This practical low cost perimeter will help detect more diseases in their early stages, as well as record their progress.

The clear hemisphere affords constant observation of the patient and also gives a sharp target without a blur. Most dark rooms, if white or dark objects are avoided, provide a background light of 30m to 50m Lamberts. A frosted hemisphere is also available for those who prefer a uniform background.

This unit is small enough and light enough to fit into most refracting rooms. It requires only 4 square feet of floor space and with the telescopic stand on casters, can be moved into position and adjusted in seconds.

#921 Universal Perimeter, complete with fiber optics, caps for reducing the target size, Red and Black grease pencils, pad of special charts, and stand with casters (specify clear or frosted hemisphere) $345.00

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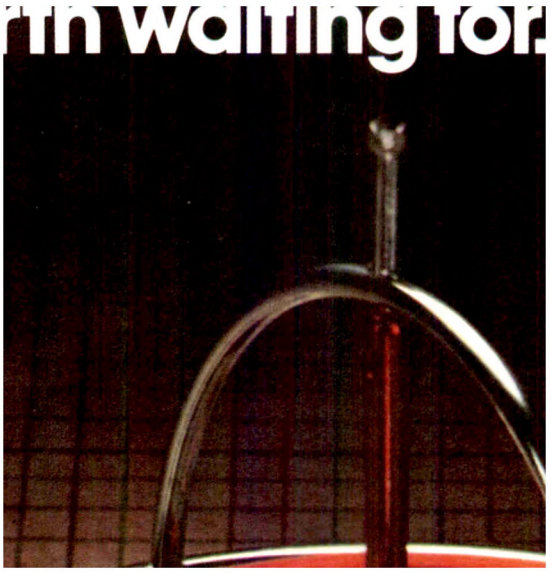
—the ultimate balance in performance plus comfort

Balance—the key to Softcon performance

Meets the needs of patient and practitioner.
Suits the needs of the daily, as well as occasional, wearer.

- No adaptation period is necessary.
- Immediate comfort, first day...all day...every or any day.
- Visual acuity of 20/20 or better, in 97% of patients studied.*
- Utilizes the convenient "cold" disinfection system.
- Available in a wide range of powers: minus, plus, high plus and plano.

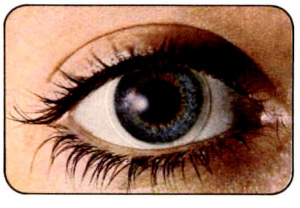
*Data on file, Soft Contact Lens Div., American Optical Corp., Southbridge, MA 01550

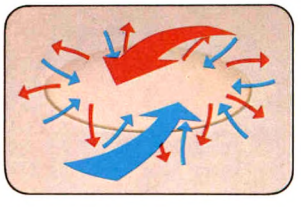

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Lens water content of 55%.
Hydroequivalence closest to that of cornea.

- Enhances lens/cornea compatibility.
- Ensures wearer comfort without compromising handling or optical properties.
- Improves permeability and fluid exchanges.
- Maintains constant environment of fresh tears due to exceptional tear pump action.





Balance—the key to Softcon fit

Computerized lens geometries.
Lathe-cut miniscleral configuration.

- Provides uniform carrier geometry for all lens powers.
- Offers "fast-fit" techniques in 6 lens geometries (3 of which will fit 80% of patients).
- Achieves superior centration and stable visual acuity.
- Permits refined power adjustment without compromising fit and comfort.



Softcon®
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See next page for full prescribing information. For further details, fill out and mail this coupon.

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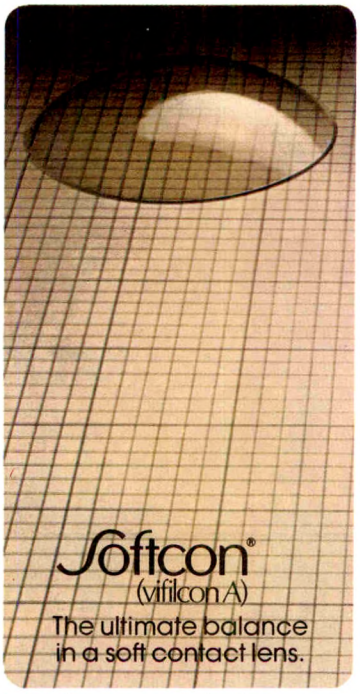
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SOFTCON® (vifilcon A) Contact Lens
Vision Correction Use

DESCRIPTION The SOFTCON (vifilcon A) Contact Lens is a hemispherical flexible transparent shell which covers the cornea and part of the sclera. The lens is composed of vifilcon A, a soft hydrophilic plastic co-polymer of 2-hydroxyethyl methacrylate and povidone, USP. The chemical name is: Poly (2-hydroxyethyl methacrylate-co-ethylene dimethacrylate-co-methacrylic acid-g-povidone). When fully hydrated, the lens contains about 55% water by weight.

INDICATIONS The SOFTCON Contact Lens is indicated for the correction of visual acuity in persons with non-diseased eyes and in aphakia. It is indicated for persons who have spherical ametropias, refractive astigmatism usually 1.50 diopters or less and/or corneal astigmatism of 2.00 diopters or less.

CONTRAINDICATIONS Presence of any active infection or inflammation of the eye, insufficient tears, corneal hypoesthesia or any systemic disease which may affect the eye adversely or be exaggerated by wearing contact lenses.

WARNINGS Medications and Eye Drops—The SOFTCON Contact Lens must be stored only in FLEXSOL® soaking solution. **NEVER USE CONVENTIONAL HARD CONTACT LENS PRODUCTS WITH THE SOFTCON CONTACT LENS.** No ophthalmic solutions or medications may be used by SOFTCON Contact Lens wearers immediately prior to or during wear of the lens. No solutions other than PREFLEX®, FLEXSOL, and NORMOL® used for cleaning and chemical disinfection may be used.

Aphakic Patients—Patients who have undergone surgery for cataract removal should not be fitted with SOFTCON Contact Lenses during the immediate post-operative period; until, in the opinion of the surgeon, the eye has healed completely.

Abrasions and Infections—If a lens becomes less comfortable to the wearer than when it was first placed on the cornea, the lens should be removed immediately, and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present, or any abnormal eye condition is observed concurrently with lens wear, the lens should be removed immediately and a clinician must be consulted.

Lens Care—WEARERS MUST ADHERE TO THE RECOMMENDED DAILY CLEANING, CARE AND DISINFECTION REGIMEN AS DESCRIBED IN THE SOFTCON WEARER'S BOOKLET. FAILURE TO ADHERE TO THE RECOMMENDED PROCEDURES MAY RESULT IN THE DEVELOPMENT OF SERIOUS EYE INFECTION.

Wearing Restriction—The lens should be removed before sleeping or swimming, and should not be worn in the presence of irritating fumes or vapors.

Visual Blurring—If unusual visual blurring occurs, the lenses must be removed until the condition subsides. If blurring persists see your eye care practitioner.

PRECAUTIONS Storage—The SOFTCON Contact Lenses must be stored only in FLEXSOL soaking solution. If left exposed to air, the lenses will dehydrate, becoming hard and easily damaged. If a lens dehydrates, it should be carefully handled and soaked again in FLEXSOL until it returns to its normal soft, supple state.

Cleaning and Disinfection—THE SOFTCON CONTACT LENS MUST BE BOTH CLEANED AND DISINFECTED DAILY. ONE PROCEDURE DOES NOT REPLACE THE OTHER.

Cleaning—Daily cleaning is necessary to remove mucus and other deposits which may have accumulated on the lens surface from normal ocular secretions, airborne debris, or handling. The lenses must be cleaned before being disinfected, as deposits on the lens tend to harden and become more difficult to remove after the lenses are disinfected.

Disinfection—Lenses must be disinfected daily according to the chemical disinfection regimen. For chemical disinfection, all three solutions, PREFLEX, FLEXSOL, and NORMOL, must be used and must be changed daily. In the event that the chemical disinfection materials are not available, the lenses should not be worn.

Hygiene—Hands must be washed, rinsed thoroughly and dried with a lint-free towel before handling the lenses. COSMETICS, lotions, soaps, oils and hand creams must not come in contact with the lenses since eye irritation may result. If aerosol sprays are used while the lenses are being worn, the eyes must be kept tightly closed until the sprays have settled.

Fluorescein—Use of fluorescein while the patient is wearing the lenses may cause the lenses to become discolored. Whenever fluorescein is used, irrigate the eyes with preserved normal saline solution, and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein irreversibly.

ADVERSE REACTIONS Serious corneal damage may result from wearing lenses which have been soaked in conventional (hard) contact lens solutions.

Eye irritation may occur within a short time after applying a hypertonic lens. Removal of the lens will relieve the irritation. Very rarely, a lens may adhere to an eye as a result of a patient sleeping with the lens on or while wearing a hypotonic lens. If a lens adheres for any reason, apply a few drops of ADAPETTES® directly to the eye and wait until the lens moves freely before removing it.

Clinical studies indicate that corneal edema as manifested by symptoms such as rainbows or halos around lights, or visual blurring may occur if lenses are worn for too long a time. Removal of the lenses and a rest period of at least one hour generally relieves these symptoms. If symptoms do not subside promptly, or if excess tearing, unusual secretions, or photophobia develop, professional consultation should be obtained.

DOSAGE AND ADMINISTRATION Fitting—Usual methods of fitting conventional (hard) contact lenses do not apply to the SOFTCON Contact Lens.

For a detailed description of the fitting technique, refer to the SOFTCON Fitting Booklet.

Wearing Schedule—The wearing schedule should be determined by the eye care practitioner. Studies have not been performed to support the safety of this lens for longer than the recommended wearing time.

Patients should wear their lenses for 8-16 hours on the day the lenses are dispensed. If patients cannot tolerate 16 hours of lens wear daily, the eyes should be examined and the lens fit re-evaluated.

Lens Care and Handling—Care must be taken on the initial visit to assure that the patient is supplied with a SOFTCON Care Kit and fully understands all proper care and handling procedures for the lenses. As with any contact lens patient, regular re-examination visits are necessary to assure ocular health and patient compliance with instructions.

How Supplied—Each lens is shipped sterile in a sealed glass vial containing buffered normal saline solution. The vial label is marked with the base curve, dioptric power, diameter and the manufacturing identification number of the lens.

Patient Care Kit—The SOFTCON Care Kit is a package required for cleaning, disinfection and storage of the lenses. It consists of the following:

- Carrying & Storage Lens Case
- PREFLEX® Sterile Cleaning Solution
- FLEXSOL® Sterile Disinfection and Storage Solution
- NORMOL® Sterile Rinsing Solution
- ADAPETTES® Sterile Lubricating Solution
- SOFTCON Wearer's Booklet

Caution: Federal law prohibits dispensing without prescription.

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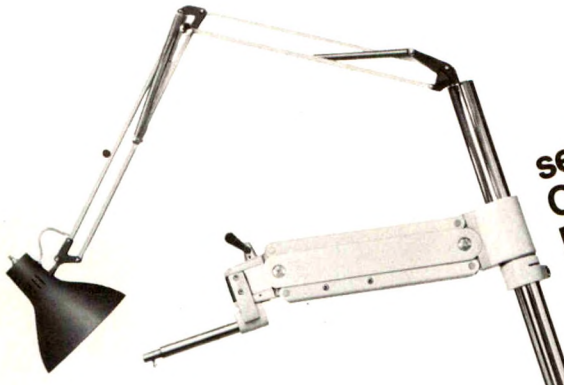
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serving the
OPHTHALMIC
PROFESSION

The new
HOV BASIC STAND
The ultimate in
efficiency, ease of
operation and
eye appeal

Designed and manufactured exclusively for the House of Vision Instrument Co., the new HOV Basic Stand will accomodate the spring-balanced, time and effort saving arms of American Optical or Reliance. It can be used in combination with the chair of your choice. Compact and sturdy with heavily weighted base and easily accessible leveling devices for uneven floors. Adjustable overhead lamp matches base cover. All wiring concealed, with electrical receptacle in base for additional diagnostic instrument transformer or charger.

Available for immediate delivery

HOV BASIC STAND for AO counter-balanced arms (arms not included)
66-500-00 ..... **$595.00**

HOV BASIC STAND for Reliance arms (arms not included)
66-500-50 ..... **$595.00**

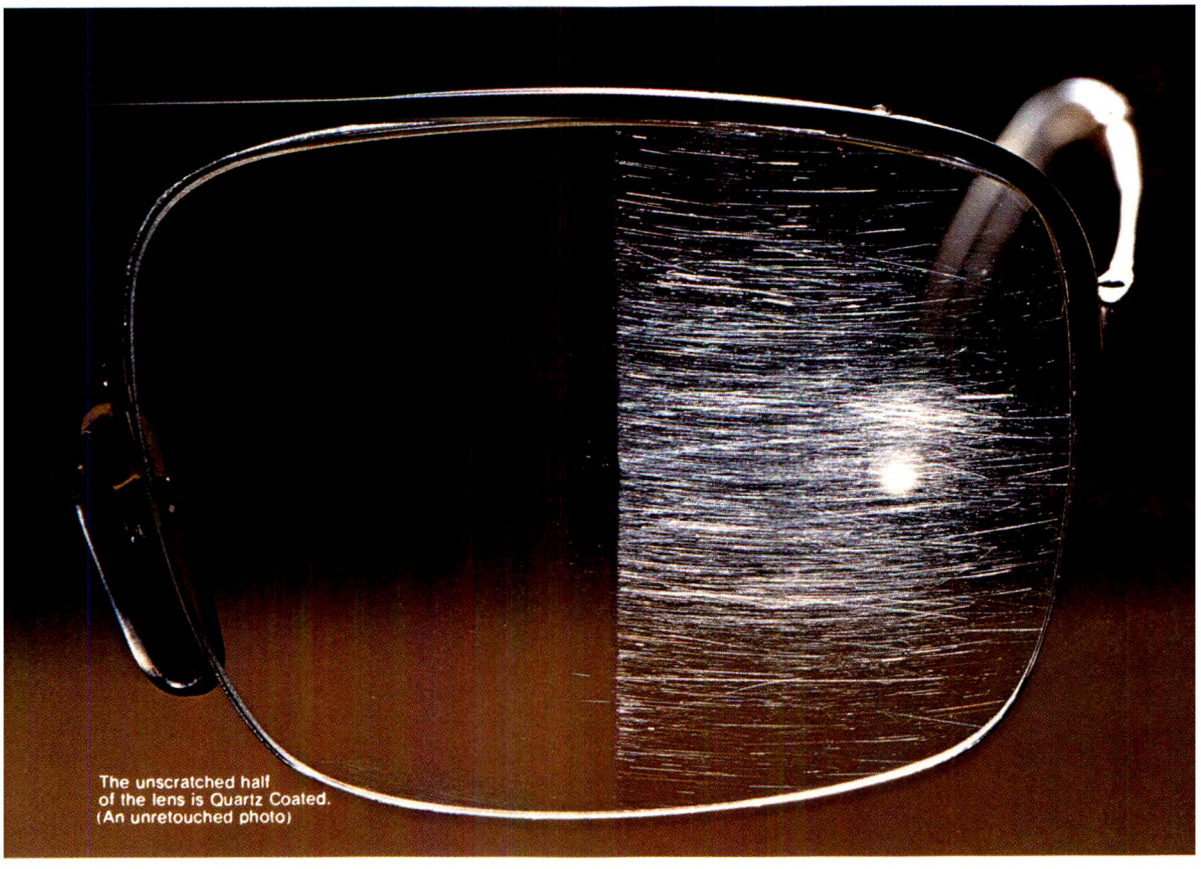


HOV BASIC STAND with instruments in place

HOUSE OF VISION INSTRUMENT CO.

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How did one side of this Hoya plastic lens get away with hardly a scratch?



If you were to rub the front surface of an ordinary resin lens a few times with scouring powder—and then do the same to the HOYA Hi-Quartz lens surface, you'd be amazed.

While the ordinary lens would be scratched, the Hi-Quartz would have come through the test virtually untouched. The secret is a quartz coating applied only to HOYA's own rigidly inspected lenses, giving them a high abrasion resistance* (Since over 95% of all scratches occur on the front surface of a lens, Hi-Quartz lenses are coated only on the convex side.) This means the lenses can take a lot of punishment.

Hi-Quartz also has a special multiple layer coating that increases light transmittance to nearly 96%, against the 92% of ordinary resin lenses. So ghost images and reflections are reduced. HOYA resin lenses coated with Hi-Quartz also have durability, because the quartz and multiple coatings are firmly bonded together to the surface of the lens.

As an easy guide, the following types of resin lenses can be coated with Hi-Quartz: Single Vision; Flat Top 22, 25, 28; Round 22. These types of resin lenses cannot be coated with Hi-Quartz: Trifocal and Executive.

Finally, Hi-Quartz has all the advantages of ordinary resin lenses, including safety, lightness and ability to be dyed. (Dyeing must be done before the quartz coating takes place.)

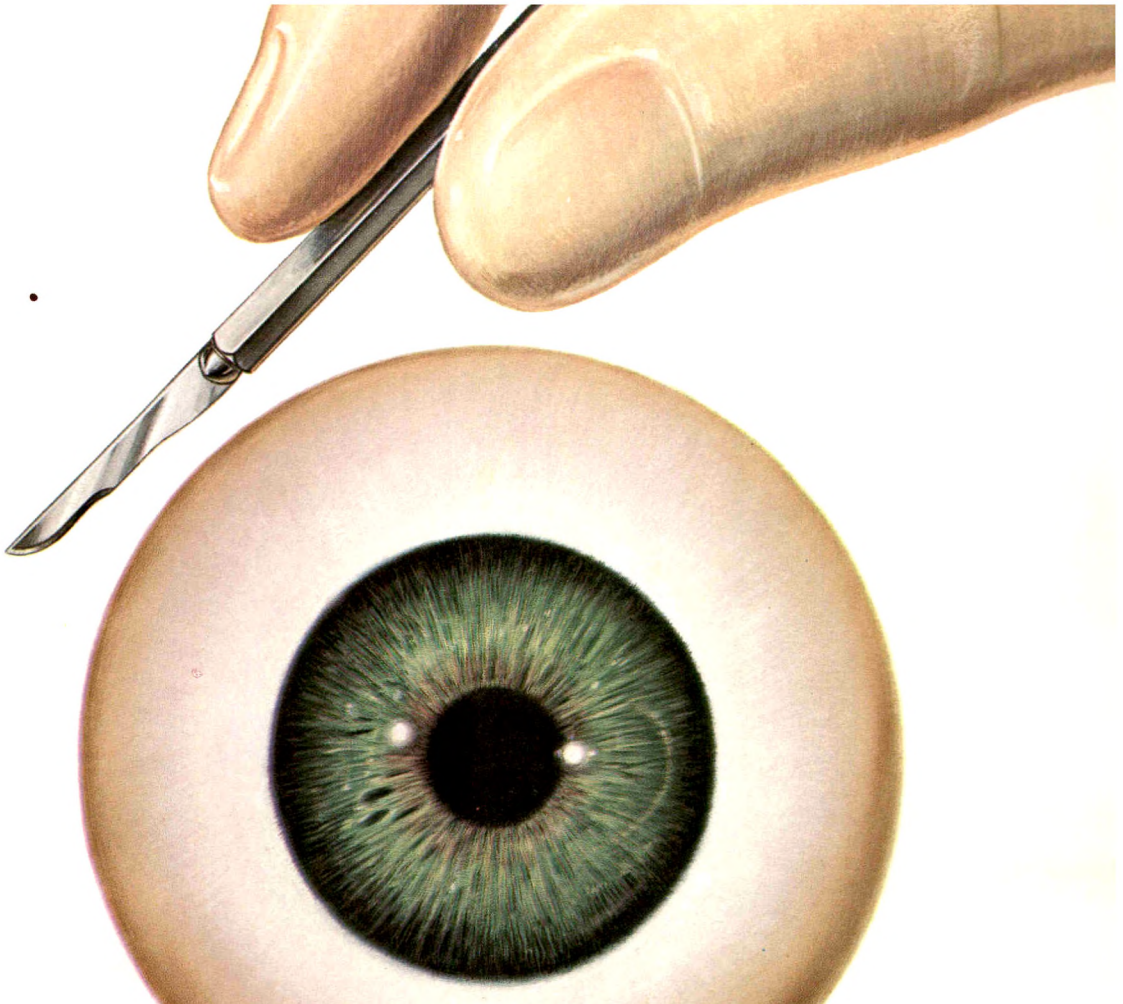
HOYA's Hi-Quartz lens. When it comes to quality products HOYA hasn't even begun to scratch the surface.

HOYA LENS

HOYA LENS OF AMERICA, INC.

*HOYA cannot accept cut or uncut lenses sent into the Torrance full prescription laboratory due to possible lens imperfections that could interfere with the quartz.

To place your order, call or write: HOYA LENS OF AMERICA, INC., 970 Knox Street, Torrance, CA. 90502
Tel.: (213) 770-6310/Nat. WATS: (800) 421-1993/Calif. WATS: (800) 262-1587



In glaucoma, the last step before surgery

When chronic glaucoma becomes refractory to acetazolamide and miotics, consider NEPTAZANE before resorting to surgery. A significant number of patients no longer responding to acetazolamide have been controlled by methazolamide.[1] There are differences, too, when it comes to side effects, since many patients intolerant to acetazolamide may be maintained on methazolamide. So whether the problem is inadequate I.O.P. control or drug intolerance, NEPTAZANE is worth a trial before surgery.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: For adjunctive treatment of chronic simple (open angle) glaucoma, secondary glaucoma, and preoperatively in acute angle closure glaucoma where delay of surgery is desired in order to lower intraocular pressure.

Contraindications: Severe or absolute glaucoma and chronic noncongestive angle closure glaucoma. Of doubtful use in glaucoma due to severe peripheral anterior synechiae or hemorrhagic glaucoma. Adrenocortical, hepatic, or renal insufficiency; electrolyte imbalance state, e.g., hyperchloremic acidosis; sodium and potassium depletion states.

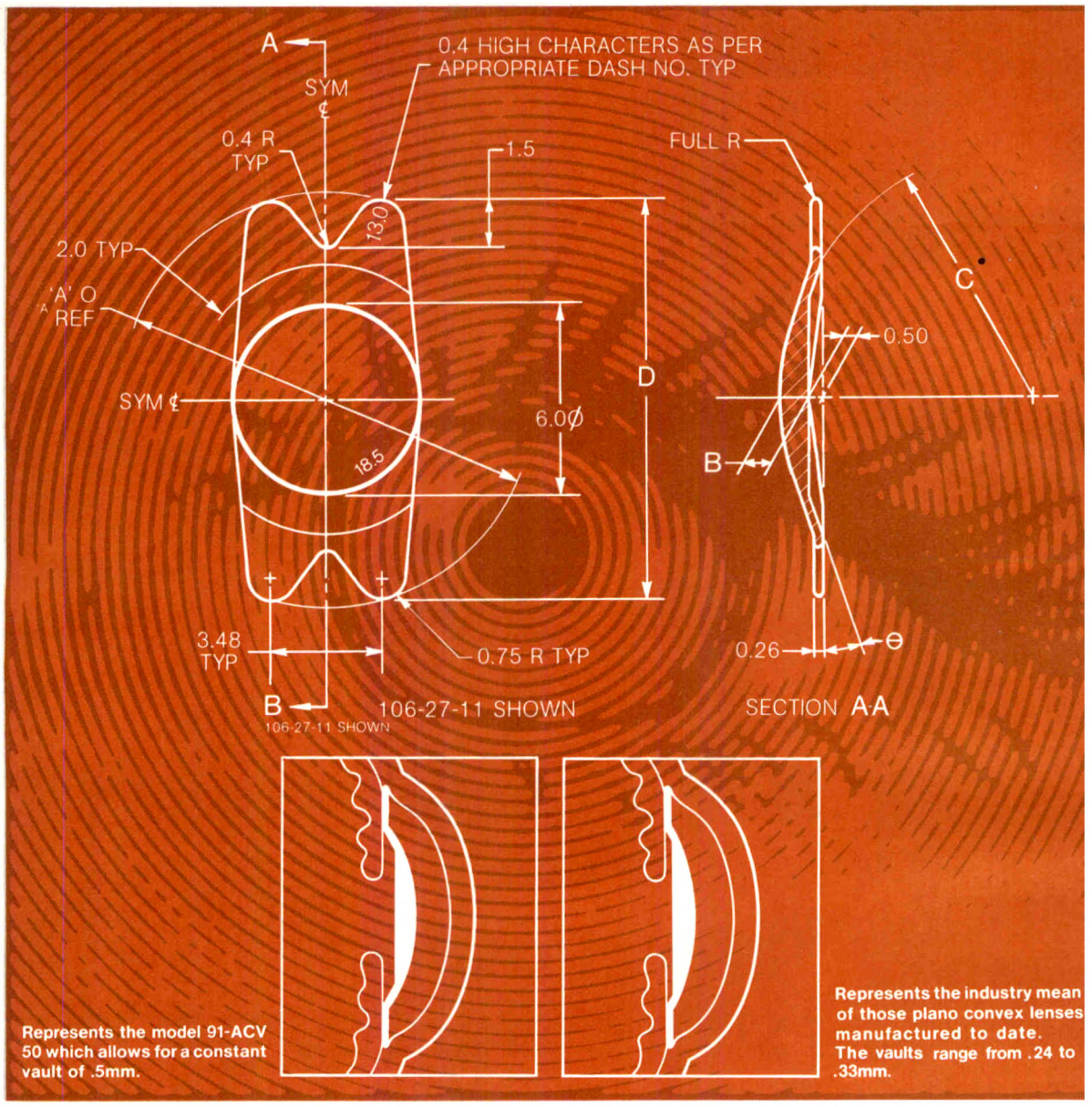
Warnings: Although teratogenic effects demonstrated in rats at high doses have not been evidenced in humans, Methazolamide should not be used in women of childbearing potential or in pregnancy, especially in the first trimester, unless the expected benefits outweigh potential adverse effects.

Precautions: Use with caution in patients with cirrhosis or hepatic insufficiency to forestall hepatic coma; those on steroid therapy; those with pulmonary obstruction or emphysema to avoid acidosis. Electrolyte balance should be maintained. Although not reported thus far with this drug, reactions common to sulfonamide derivatives, such as fever, leukopenia, hemolytic anemia, bone marrow depression or renal calculi, may occur.

Adverse Reactions (relatively mild and disappear on withdrawal or dosage adjustment): anorexia, nausea, vomiting; malaise, fatigue or drowsiness, headache; vertigo, mental confusion, depression, paresthesias. Urinary citrate excretion and uric acid output is decreased during use of this drug, but urinary calculi have not been reported.

NEPTAZANE®
METHAZOLAMIDE Tablets 50 mg.

Lederle LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York 10965



The 91-ACV50 Lens

Design Improvements to the European Style Lens

Iris Chafe–The direct cause has yet to be defined, the effect has been reported. In those instances not medically manageable, micro-hyphema, intermittant elevated pressure and uveitis have been the cause of lens removal.

The response from those physicians experiencing complications has been rapid and informative. The major point raised was the proximity of the posterior surface of the lens to the iris. The second being the edge finish. It was also noted, that even in those lenses with what appeared to be good edge finish, the above mentioned phenomenon still presented itself.

As an added note, the area of the lens used to change the diagonal length dimension entered into the design considerations, as most manufacturers routinely extend the footplate length, thus adding to the iris contact area. By using the strut area to increase or decrease the lens length, a constant iris touch area is maintained as well as a minimum of .5 millimeters vault. Even with a vaulting of .5 millimeters, a mean height of only 1.3 millimeters to the apex of the front surface is easily achieved.

By applying the same optical polish techniques used on the lens surface to that of the edge (in addition to increasing the distance between the posterior side of the lens and the iris face) we feel that we have responded in full to tho recommendations on anteri chamber lens design made to

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The Precision Optics Peop

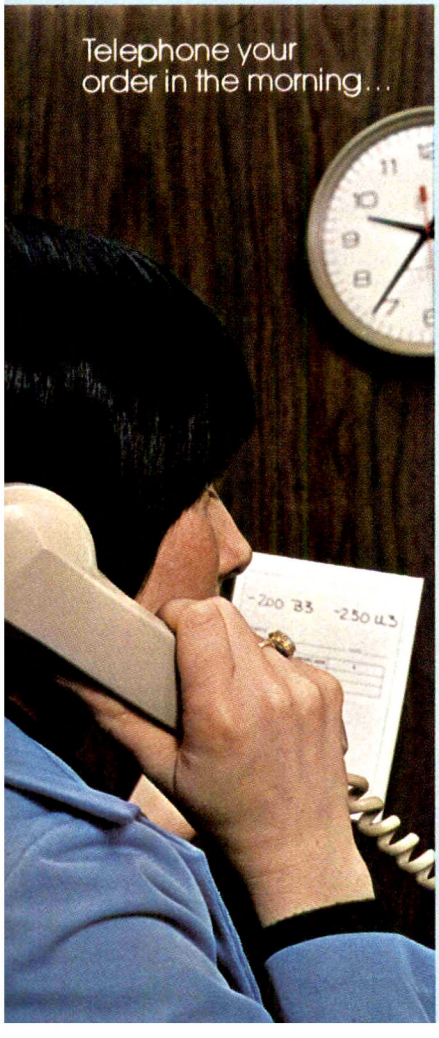
Be sure to visit our booths No.'s 331 and 430 during the AAO in Kanas City.

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How can we offer same day shipping on your SOFLENS® Contact Lens orders? (polymacon)





Spin-casting.

That's the answer. Our revolutionary spin-casting technique allows us to manufacture large quantities of lenses quickly and dependably so we can stock a full inventory of all powers and series of SOFLENS Contact Lenses. The lenses you order will be right in stock and can be shipped to you the very day you order them. This means convenience for you and for your patients.

FOR THE OPTIMIZER CONSIGNMENT PROGRAM

Because we can produce high-quality lenses in large volume, we can offer you in-office inventory programs like the OPTIMIZER consignment program. Under the OPTIMIZER program we consign you all the lenses you need to fit new patients and provide replacement lenses directly from stock. We set up the system in your office, service and maintain the inventory and do most of the paperwork for you. The only lenses you buy are the lenses you dispense. With the OPTIMIZER, you get big inventory convenience at small cost.

FOR HIGH REPRODUCIBILITY

The spin-casting process offers consistency from power to power and series to series. With SOFLENS Contact Lenses you get repeatable lens performance time after time. This saves you fitting time and makes lens replacements as easy as picking up the phone.

Same day shipping ... the OPTIMIZER program ... high reproducibility for easier fitting. Spin-cast SOFLENS Contact Lenses can make your contact lens practice easier. For more information contact your SOFLENS Representative or call, toll-free, 800-828-9030 (New York, 800-462-1720).

BAUSCH & LOMB
SOFLENS®
(polymacon)
Contact Lenses

Consistency you can count on.

Please see next page for full prescribing information.



BAUSCH & LOMB SOFLENS® (polymacon) Contact Lenses

VISION CORRECTION USE

DESCRIPTION: The SOFLENS® (polymacon) Contact Lens is a hemispherical flexible shell which covers the cornea and may cover a portion of the adjacent sclera. It consists of 61.4% poly (2-hydroxyethyl methacrylate) and 38.6% water by weight when immersed in normal saline. The material has a refractive index of 1.43 and the lens has a visible light transmittance of more than 97%.

ACTIONS: In its hydrated state a SOFLENS® (polymacon) Contact Lens is soft and pliable. When placed on the human cornea, the hydrated SOFLENS® (polymacon) Contact Lens acts as a refracting medium to compensate spherical ametropias.

INDICATIONS: SOFLENS® (polymacon) Contact Lenses are indicated for vision correction use in persons with non-diseased eyes and in aphakia.

CONTRAINDICATIONS: SOFLENS® (polymacon) Contact Lenses are contraindicated in the presence of any active untreated infection or abnormality of the anterior segment of the eye with the exception of ametropia and aphakia.

WARNINGS: Abrasions and Infections—If a lens becomes less comfortable than it was when first placed on the wearer's cornea, the lens should be removed immediately and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present, or any abnormal eye condition is observed concurrent with lens wear, the lens should be removed immediately and a physician consulted.

Infectious corneal ulcers have been reported, usually associated with failure to follow the recommended procedures for care of the lenses.

Aphakic Patients—Aphakic patients should not be fitted with SOFLENS® (polymacon) Contact Lenses during the postoperative period until, in the opinion of the surgeon, the eye has healed completely.

Lens Sanitation and Handling—Persons who require only vision correction and who would not, or could not, adhere to the recommended daily sanitary care of SOFLENS® (polymacon) Contact Lenses or who are unable to place and remove the lenses should not be provided with them. Failure to follow handling and sanitation instructions could lead to serious eye infections which might result in corneal ulcers.

Malfunction and rusting of the metal interior of the Aseptor®—Patient Unit as well as discoloration and cracking of the lens case has been reported after varying periods of use. If such occurs, appropriate replacement is indicated to avoid interference with the disinfection procedure.

Medicants and Eye Drops—When the lenses are used by persons requiring only vision correction no ophthalmic solutions or medicants, including conventional contact lens solutions and eye drops, should be used by SOFLENS® (polymacon) Contact Lens wearers prior to placement, or while the lens is in place, on the eye. Also, no solutions, including conventional contact lens solutions other than normal saline, and the solution made from the SOFLENS™ Enzymatic Contact Lens Cleaning Tablets are to be used on a SOFLENS® (polymacon) Contact Lens when the lens is off the eye.

Wearing Restrictions—SOFLENS® (polymacon) Contact Lenses when used only for vision correction should be removed before sleeping or swimming and in the presence of noxious and irritating vapors. Insufficient lacrimal secretions or hypoesthesia may be restricting factors to the wearing of soft contact lenses.

PRECAUTIONS: Storage—SOFLENS® (polymacon) Contact Lenses must be stored ONLY in normal saline solution. If left exposed to air, the lenses will dehydrate, become brittle, and break readily. If a lens dehydrates, it should be resoaked in normal saline solution until it returns to its soft, pliable state which may take as long as forty minutes.

Fresh normal saline must be prepared **daily** for cleaning and storing the lenses. The carrying case must be emptied and refilled with fresh normal saline solution just before disinfecting the lenses.

The one ounce squeeze bottle is intended for preparation of normal saline only. As this saline is not aseptic, it should not be used to clean a lens that is to be replaced immediately on the eye, nor should this solution ever be placed in the eye. If the patient wishes to remove a lens, clean it, or wet it and replace it on the eye, the solution in the carrying case should be used, as it will have been disinfected.

Hygiene—Hands must be washed, rinsed thoroughly, and dried with a lint-free towel before handling the lenses.

Cosmetics, lotions, soaps, and creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the hair spray has settled.

Handling—A SOFLENS® (polymacon) Contact Lens may be damaged by nicking or tearing if care is not exercised during placement on or removal from the eye, replacing or removing it from the carrying case or in the cleaning process. Lenses must be placed very carefully in the carrying case to avoid damaging the edges of the lenses.

Disinfecting—Fresh normal saline must be prepared daily. After removal from the eye, the SOFLENS® (polymacon) Contact Lens must be irrigated with saline and rubbed gently to remove mucus and film from the lens' surface. The carrying case must be emptied and refilled with fresh normal saline solution just before disinfecting the lenses.

The causes and nature of deposits formed on the surfaces of some lenses have not been completely evaluated. However, some coatings are known to be proteinaceous and others may be oily or greasy film from extraneous agents, such as hair spray or other cosmetics, or from the patient's own lacrimal secretions. Many wearers experience little or no difficulty with such deposits. However, occasionally a wearer, who tends to secrete unusually large amounts of mucus in the lacrimal fluid, may experience a build-up of these deposits within a relatively few weeks, despite adequate cleaning measures. If surface accumulations of non-removable materials persist, professional care should be obtained promptly.

Deposits, characterized as medium or heavy, were found on 17.5 percent of a population of lenses worn an average of 11.2 months, including lenses worn as long as thirty months. The occurrence of these deposits appeared to increase with the duration of lens use. These medium or heavy deposits, when they do exist, can be detected by means of a slit lamp biomicroscope examination. Light deposits, unrelated to length of lens use and of no apparent clinical significance, were observed on approximately one-half of the lenses studied.

The SOFLENS® Carrying Case should be washed at least once a week with hot water and then rinsed thoroughly with distilled water. Soap or other cleaners should never be used to clean the carrying case.

In order to remove protein deposits which may form on the lenses, wearers should use the SOFLENS™ Enzymatic Contact Lens Cleaning Tablets according to the directions for use which accompany the tablets. To prevent the formation of the protein deposits, patients should use the SOFLENS™ Enzymatic Contact Lens Cleaning Tablets once a week or as directed by the practitioner.

Disinfecting with an Aseptor® or Aseptron™ Disinfecting Unit is necessary to kill microorganisms.

If an Aseptor® or Aseptron™ Unit is not available, the lenses may be disinfected by boiling them in their carrying case in a pan of water for 15 minutes. When this boiling method of disinfection is used, the lenses can be damaged if the boiling water is allowed to completely evaporate.

The carrying case must **always** be tightly closed before disinfecting to prevent leakage of the saline from the case and subsequent dehydration of the lenses.

Fluorescein—Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with sterile normal saline solution and wait at least one hour before replacing the lenses. Earlier replacement may cause the lenses to absorb residual fluorescein.

ADVERSE REACTIONS: Serious corneal damage may result from wearing a SOFLENS® (polymacon) Contact Lens which has been soaked in a conventional contact lens solution.

Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation.

A lens adheres very rarely to an eye as a result of sleeping with the lens on, or wearing a hypotonic lens. If a lens adheres for any reason, apply normal saline and wait until the lens moves freely before removing it.

Clinical studies indicate that corneal edema, as manifested by symptoms such as rainbows, halos around lights, or foggy vision, may occur in less than 5% of SOFLENS® (polymacon) Contact Lens wearers. If these symptoms occur, the lenses should be removed and professional consultation obtained.

Excessive tearing, unusual eye secretions, and photophobia are not normal. If these symptoms occur, the patient should be examined to determine their cause.

A faint blue haze, believed to be located in Descemet's membrane, has been reported in the Spokane, Washington area. As yet, the cause is unknown and the phenomenon has not been found elsewhere. The wearers report no subjective symptoms and there is no detectable effect on their visual acuity. There have been approximately 29 cases, and in 10 of these patients the blue haze has cleared or is in various stages of regression.

Neovascularization of the cornea has been observed in some aphakic patients fitted with the SOFLENS® (polymacon) Contact Lens, which may require discontinuation of the lens. Medical consultation should be obtained in such an instance.

LENS REPLACEMENT: Various studies have been conducted to determine the frequency of lens replacements and the reasons for those replacements. These studies show that during the first four months of wear, approximately one quarter of the lenses initially dispensed are replaced; the principal reason for these replacements is lens damage. Lenses are more apt to be damaged while new wearers are learning the prescribed handling and care techniques. After the initial four months of wear, the average lens replacement rate has been found to be approximately one lens per wearer per year. Lens loss, damage and surface deposits were the major causes for lens replacements.

DOSAGE AND ADMINISTRATION: Conventional methods of fitting contact lenses do not apply to SOFLENS® (polymacon) Contact Lenses. For a detailed description of the fitting technique, refer to the SOFLENS Fitting Guide, copies of which are available from: SOFLENS Division, Bausch & Lomb Incorporated, Rochester, N.Y. 14602.

When the lenses are used only for vision correction, there may be a tendency for the patient to overwear the lenses initially. Therefore, the importance of adhering to the following initial daily wearing schedule should be stressed to these patients:

Day	Wear Time (hours)	Rest Period (hours)	Wear Time (hours)	Rest Period (hours)	Wear Time (hours)
1	3	1	3	1	3
2	3	1	3	1	3
3	4	1	4	1	4
4	4	1	4	1	4
5	6	1	6	1	4
6	6	1	6	1	4
7	8	1	8		
8	8	1	8		
9	8	1	8		
10	10	1	balance of the waking hours*		
11	12	1	balance of the waking hours*		
12	14	1	balance of the waking hours*		

*Lenses used only for vision correction should never be worn 24 hours a day.

When lenses are dispensed for vision correction, the wearer must be supplied with a lens care kit and must fully understand all lens care and handling instructions. As with any contact lens, regular recall visits are necessary to assure corneal health and wearer compliance with instructions.

HOW SUPPLIED: Each lens is supplied sterile in a glass vial containing sterile normal saline solution. The glass vial is marked with the manufacturing lot number of the lens and the dioptric power (black for plus power lenses; red for minus; gold or white for plano).

Caution: Federal Law Prohibits Dispensing Without a Prescription.

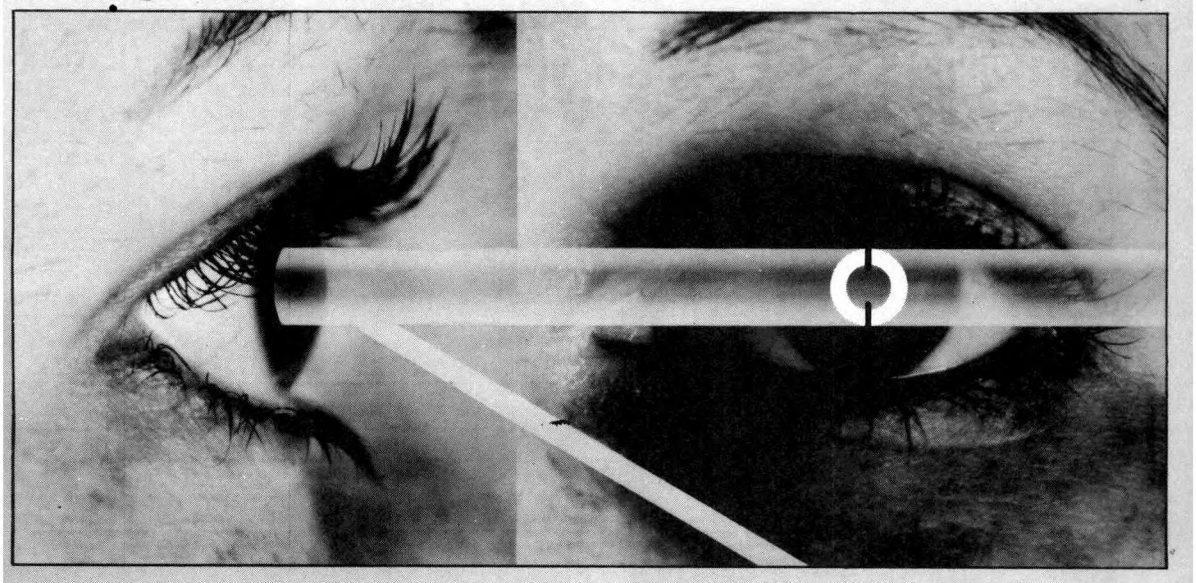
The SOFLENS® Care Kit is available for lens disinfecting, cleaning, and storage.

Complete information on lenses and accessory products can be found in the current SOFLENS Fitting Guide or price list.

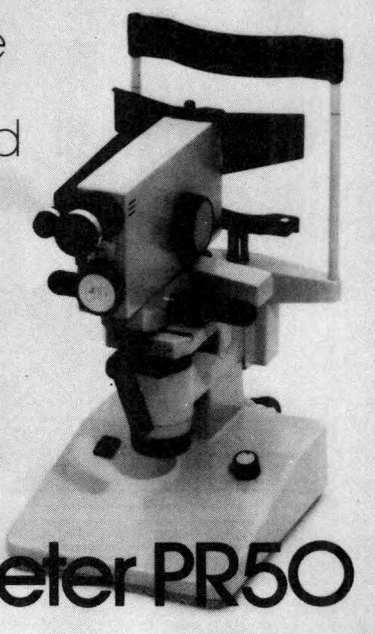
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SOFLENS DIVISION
Rochester, N.Y. 14602

Unique Instrument Objectively Measures Refractive Error And Astigmatism Quickly And Accurately



Procedure is more comfortable for the patient, seldom requires mydriasis... and the technique is quickly mastered by practitioner or paramedic.



The Rodenstock Refractometer PR 50—now distributed by Coburn Optical Industries Inc.—is an economical instrument which gives accurate refractive readings and measures astigmatism, giving precise axis location of the correcting cylinder in just a few minutes.

By quickly measuring the degree of refractive error, the Rodenstock Refractometer PR 50 greatly shortens the time for objective refraction... allows practitioner or paramedic to serve patients more conveniently.

Rodenstock Refractometer PR50

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Please arrange a demonstration of the Rodenstock Refractometer PR 50 in my office.

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City _____ State _____ Zip _____

Aquaflex®
(tetrafilcon A)
Hydrophilic Contact Lens



Outstanding Visual Acuity



Optimum Centration



Predictable Fit

The Performance Story.

Soft contact lens performance that meets your exacting professional needs.

tstanding Visual Acuity

ajor benefit of Aquaflex® (tetrafilcon A) rophilic Contact Lenses is excellent visual ty. Clinical data revealed that 88% of the rers achieved 20/20 vision or better, with attaining 20/25 or better.[1] Practitioners rted that Aquaflex lenses often corrected e astigmatism and gave sharper vision other soft lenses.[1] This quality of ormance is due to a unique combination phisticated lens design, special lens erial and the "Vault" system of fitting.

timum Centration

nical study showed that over 96% of aflex contact lens wearers achieved num centration.[1] By centering so well, aflex lenses virtually eliminate the induced gmatism and lessened visual acuity lting from decentered lenses.[2] Precise ration helps in attaining a good fit with full eal coverage and maximum visual acuity, e permitting proper corneal respiration.

dictable Fit

omplicated graphs, charts and ulations, because the Aquaflex "Vault" em reduces fitting variables to just one... ens "Vault". Only 5 Vaults are needed to fit aflex lenses;[3] and in clinical studies more 90% of the patients were fitted with just 3 ese Vaults.[1] The bicurve, lathe-cut lens truction, with spherical front and back aces, promotes reliable fit independent of er; and the large posterior optical zone s stability of vision with lens movement.

Additional Advantages

Other significant attributes of the Aquaflex® (tetrafilcon A) lens, contributing to practitioner success and patient acceptance, are: reliable over-refraction,[2,4] ease in handling, durability, excellent reproducibility[2] and exceptionally high standards of quality assurance, including 100% wet inspection. A study has shown that less than 5% of lenses shipped were returned because of questionable performance, discomfort, damage or defects.[1] The fitting procedure is simple and fast.[4] You can fit from a small diagnostic set, or use a dispensing inventory. Lenses may be ordered by a toll-free phone call, and UCO Optics' service is quick and dependable. More and more practitioners are using Aquaflex lenses every day. Shouldn't you?

Aquaflex®
(tetrafilcon A)
Hydrophilic Contact Lens

For more information and a copy of the Professional Fitting Guide, mail the coupon. Or, phone toll-free 800-828-4580 (in N.Y.State 800-462-4332).

See following page for full prescribing information.

ta on file: UCO Optics, Inc., Scottsville, N.Y. 14546
rrison, Robert J.: International Contact Lens Clinic, ner 1976
uber, Ellis & Gordon, Stanley: Contact Lens Forum, ary 1977
eenspoon, Morton K.: Contact Lens Forum, mber 1977.

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UCO Optics, Inc. Aquaflex® Division
711 North Road, Scottsville, N.Y. 14546

I'm interested in Aquaflex® (tetrafilcon A) Hydrophilic Contact Lenses.
Send full information.
Have your representative call.

Name
Address
City
State
Zip
Phone

AJO 10/7

Aquaflex®
(tetrafilcon A)
Hydrophilic Contact Lens

DESCRIPTION
AQUAFLEX® (tetrafilcon A) Hydrophilic Contact Lens is a hemispherical shell which covers the cornea and may cover a portion of the adjacent sclera. The lens material, tetrafilcon A, is a hydrophilic random terpolymer of 2-hydroxyethyl-methacrylate, N-vinyl-2-pyrrolidone and methylmethacrylate. The polymer is a three-dimensional network of terpolymer chains joined by divinylbenzene cross-links. It consists of 57.5% tetrafilcon A and 42.5% water by weight when fully hydrated in normal saline solution. Lenses have a nominal diameter of 13 mm.

ACTIONS
In its hydrated state the AQUAFLEX® Hydrophilic Contact Lens is soft and pliable. When dry, the lens becomes hard and brittle. These states are completely reversible and a lens which has been permitted to dry out will recover all of its hydrated properties when placed in normal saline for a period of two hours. When placed on the human cornea the hydrated lens acts as a refracting medium to compensate spherical ametropias. The material has a refractive index of 1.43 and the lens has a visible light transmittance greater than 97%.

INDICATIONS
AQUAFLEX® Hydrophilic Contact Lenses are indicated for the correction of vision in persons with non-diseased eyes who have spherical ametropias, corneal astigmatism of 2.50 diopters or less and/or refractive astigmatism of 2.00 diopters or less.

CONTRAINDICATIONS
AQUAFLEX® Hydrophilic Contact Lenses are contraindicated in the presence of any of the following conditions: (1) Acute and subacute inflammation of the anterior segment of the eye. (2) Any eye disease which affects the cornea or conjunctiva. (3) Insufficiency of lacrimal secretion. (4) Corneal hypoesthesia. (5) Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses.

WARNINGS
Medications and Eye Drops: AQUAFLEX® Lenses must be stored in an appropriate solution when off the eyes, the type of solution being dependent on the system used for disinfection. When the lenses are disinfected with the thermal disinfection system, they may be stored *only* in BOILnSOAK® Solution (sterile buffered isotonic solution containing boric acid, sodium borate, sodium chloride 0.7%, preserved with Thimerosal (Lilly) 0.001% and edetate disodium 0.1%). When lenses are disinfected with the chemical disinfection system, they may be stored *only* in FLEXSOL® Disinfection and Storage Solution (sterile buffered isotonic solution of sodium chloride, sodium borate, boric acid, polyvinylpyrrolidone, polyoxyethylene and polyoxypropylene, preserved with Thimerosal (Lilly) 0.001%, chlorhexidine 0.005% and edetate disodium 0.1%).

No ophthalmic solutions or medications, including hard contact lens solutions, can be used by AQUAFLEX® Lens wearers prior to or while the lenses are in place on the eyes. Also, no solutions, including hard contact lens solutions, other than BOILnSOAK® Solution or FLEXSOL® Solution may be used on AQUAFLEX® Lenses when they are off of the eyes.

Since liquids and vapors may be absorbed by AQUAFLEX® Lenses, they should not be placed in the mouth for wetting, nor wiped with a cloth or tissue.

Abrasions and Infections: If a lens becomes less comfortable than it was when first placed on the wearer's cornea, the lens should be removed immediately and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present, or any abnormal eye condition is observed concurrently with lens wear, the lens should be removed immediately and a physician consulted.

Wearing Restrictions: AQUAFLEX® (tetrafilcon A) Hydrophilic Contact Lenses should not be worn while swimming, sleeping, or in the presence of irritating fumes or vapors.

Visual Blurring: If visual blurring occurs, the lens must be removed until the condition subsides.

Lens Care Regimen: Patients must adhere to the recommended daily care procedures for AQUAFLEX® Hydrophilic Contact Lenses. Failure to follow this procedure may result in the development of serious ocular infections.

PRECAUTIONS
Storage: AQUAFLEX® Lenses may be stored *only* in the appropriate storage solution: BOILnSOAK® Solution or FLEXSOL® Solution depending on disinfecting methods used. If left exposed to air, the lenses will dehydrate, become brittle and break readily. If a lens dehydrates, it should be soaked in either BOILnSOAK® Solution or FLEXSOL® Solution until it returns to a soft, supple state.

Cleaning and Disinfecting: AQUAFLEX® Lenses *must* be both cleaned and disinfected daily. Separate procedures and products are needed to clean and to disinfect. Two methods of disinfection, thermal or chemical, have been shown to be equally effective. The choice of disinfection system should be made in consultation with your eye care practitioner.

Cleaning: Daily cleaning is necessary to remove mucus and other deposits which may have accumulated on the lens surface. Each time the lenses are removed from the wearer's eyes, both surfaces of the lenses must be cleaned using several drops of PREFLEX® Cleaning Solution (sterile buffered isotonic aqueous solution consisting of sodium phosphates, sodium chloride, tyloxapol, hydroxyethylcellulose and polyvinyl alcohol with Thimerosal (Lilly) 0.004% and edetate disodium 0.2% added as preservatives). Lenses must be cleaned before they are disinfected, as deposits on the lenses tend to harden and become more difficult to remove after the lenses are disinfected.

Disinfecting: AQUAFLEX® Lenses may be disinfected with either a heat or chemical regimen. One method or the other must be selected, but not both. The user must not alternate between methods.

Thermal Disinfection Method: AQUAFLEX® Lenses may be effectively disinfected after cleaning with PREFLEX® Cleaning Solution with use of the AQUASEPT® Patient Unit and BOILnSOAK® Solution. Fresh BOILnSOAK® Solution must be used for daily storage of lenses or each time the lens is stored. The AQUASEPT® Patient Unit requires distilled water. The AQUAFLEX® Lens Storage Containers must be emptied and filled with fresh BOILnSOAK® Solution just prior to disinfecting the lenses.

Chemical Disinfection: Disinfection with PREFLEX® Cleaning Solution, FLEXSOL® Solution and NORMOL® Rinsing Solution (sterile buffered isotonic aqueous solution of sodium chloride, sodium borate and boric acid, preserved with Thimerosal (Lilly) 0.001%, edetate disodium 0.1% and chlorhexidine 0.005%) has also been shown to be an effective disinfection system for daily care of AQUAFLEX® Lenses. AQUAFLEX® Lenses must be cleaned and rinsed daily (or after wearing) with PREFLEX® Cleaning Solution and NORMOL® Rinsing Solution. The AQUAFLEX® Lens Storage Containers must be emptied and refilled with fresh FLEXSOL® Solution each time the lens is stored. Fresh FLEXSOL® Solution must be used daily for storage and disinfection. WARNING: DO NOT MIX OR ALTERNATE THE DISINFECTION AND STORAGE SYSTEMS. FLEXSOL® SOLUTION SHOULD NOT BE USED WITH HEAT.

Hygiene: Before handling the lenses, hands must be washed, rinsed thoroughly and dried with a lint-free towel. Cosmetics, lotions, soaps, oils and hand creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the spray has settled.

Fluorescein: Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with normal saline solution and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein.

ADVERSE REACTIONS
Serious corneal damage may result from wearing lenses which may have soaked in hard contact lens solutions. Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation.

Very rarely a lens may adhere to an eye as a result of a patient sleeping with the lens on, or as a result of wearing a hypotonic lens. If a lens adheres for any reason, the patient may be instructed to apply a few drops of BOILnSOAK® Solution (if using a thermal disinfection regimen) or ADAPETTES® Lubricating Solution (buffered isotonic aqueous solution containing ADSORBOBASE® [polyvinyl-pyrrolidone with other water soluble polymers] with Thimerosal (Lilly) 0.004% and edetate disodium 0.1% added as preservatives) (If using a chemical disinfection regimen), and wait until the lens moves freely before removing it.

Clinical studies indicate that corneal edema as manifested by symptoms such as rainbows or halos around light or visual blurring may occur if lenses are worn continuously for too long a time. Removal of the lenses and a rest period of at least one hour generally relieve these symptoms. If symptoms do not subside promptly, professional consultation should be obtained.

Excessive tearing, unusual eye secretions and photophobia are not normal; if these symptoms occur, the patient should be examined to determine their cause.

DOSAGE AND ADMINISTRATION
Fitting: Conventional methods of fitting contact lenses do not apply to AQUAFLEX® (tetrafilcon A) Hydrophilic Contact Lenses. For a detailed description of the fitting technique, refer to the Professional Fitting Guide for AQUAFLEX® Hydrophilic Contact Lenses, copies of which are available from: UCO Optics, Inc., Scottsville, New York 14546.

Wearing Schedule: There may be a tendency for the patient to overwear the lenses initially. Therefore, the importance of adhering to the following initial daily wearing schedule should be stressed to the patient.

Day	Wear Time (*Hours*)	Rest Period (*Hours*)	Wear Time (*Hours*)
1	4	2	4
2	4	2	4
3	5	2	5
4	6	2	5
5	7	2	5
6	7	1	6
7	8	1	7
8	8	1	8
9	9	1	8
10-14	10	1	balance of
15	all waking hours		waking hours†

†lenses should never be worn 24 hours a day

Lens Care and Handling: Care must be taken on the initial visit to assure that the patient is supplied with an appropriate AQUAFLEX® Patient Care Kit and fully understands all care and handling instructions for the lenses. As with any contact lens, regular recall visits are necessary to assure patient health and compliance with instructions.

How Supplied: Each lens is supplied sterile in a glass vial containing normal saline solution. The glass vial is marked with the vault number, dioptric power, and manufacturing identification number.

The AQUAFLEX® Patient Care Kit is required for lens cleaning, disinfection and storing of the lenses. The Kit may consist of either of the following:

Thermal Disinfection Regimen

AQUAFLEX® Patient Care Kit	
AQUASEPT® Patient Unit	Catalog No. A0101
AQUAFLEX® Lens Storage Container	Catalog No. A0201
PREFLEX® Cleaning Solution	Catalog No. A1201
BOILnSOAK® Solution	Catalog No. A1301
AQUAFLEX® Patient Instruction Book	Catalog No. X0102

Chemical Disinfection Regimen

AQUAFLEX® Patient Care Kit	
AQUAFLEX® Lens Storage Container	Catalog No. A0202
PREFLEX® Cleaning Solution	Catalog No. A1201
NORMOL® Rinsing Solution	Catalog No. A1401
FLEXSOL® Disinfection and Storage Solution	Catalog No. A1501
ADAPETTES® Lubricating Solution	Catalog No. A1601
AQUAFLEX® Patient Instruction Book	Catalog No. X0102

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CAUTION: Federal law prohibits dispensing without prescription.

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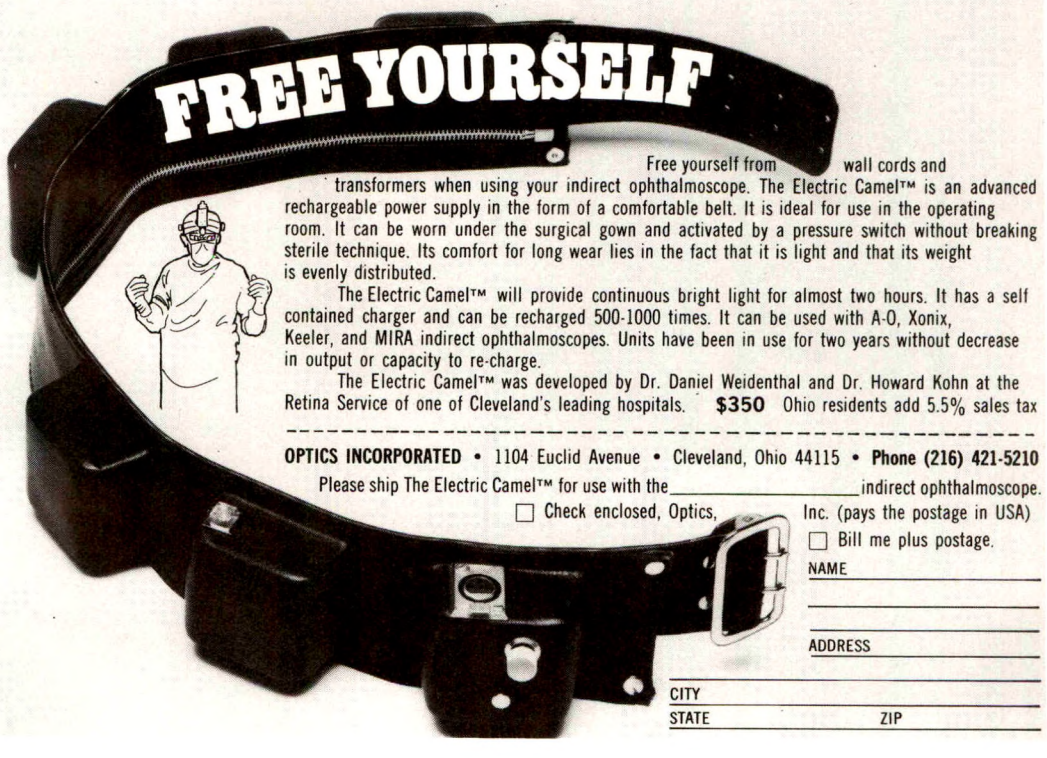
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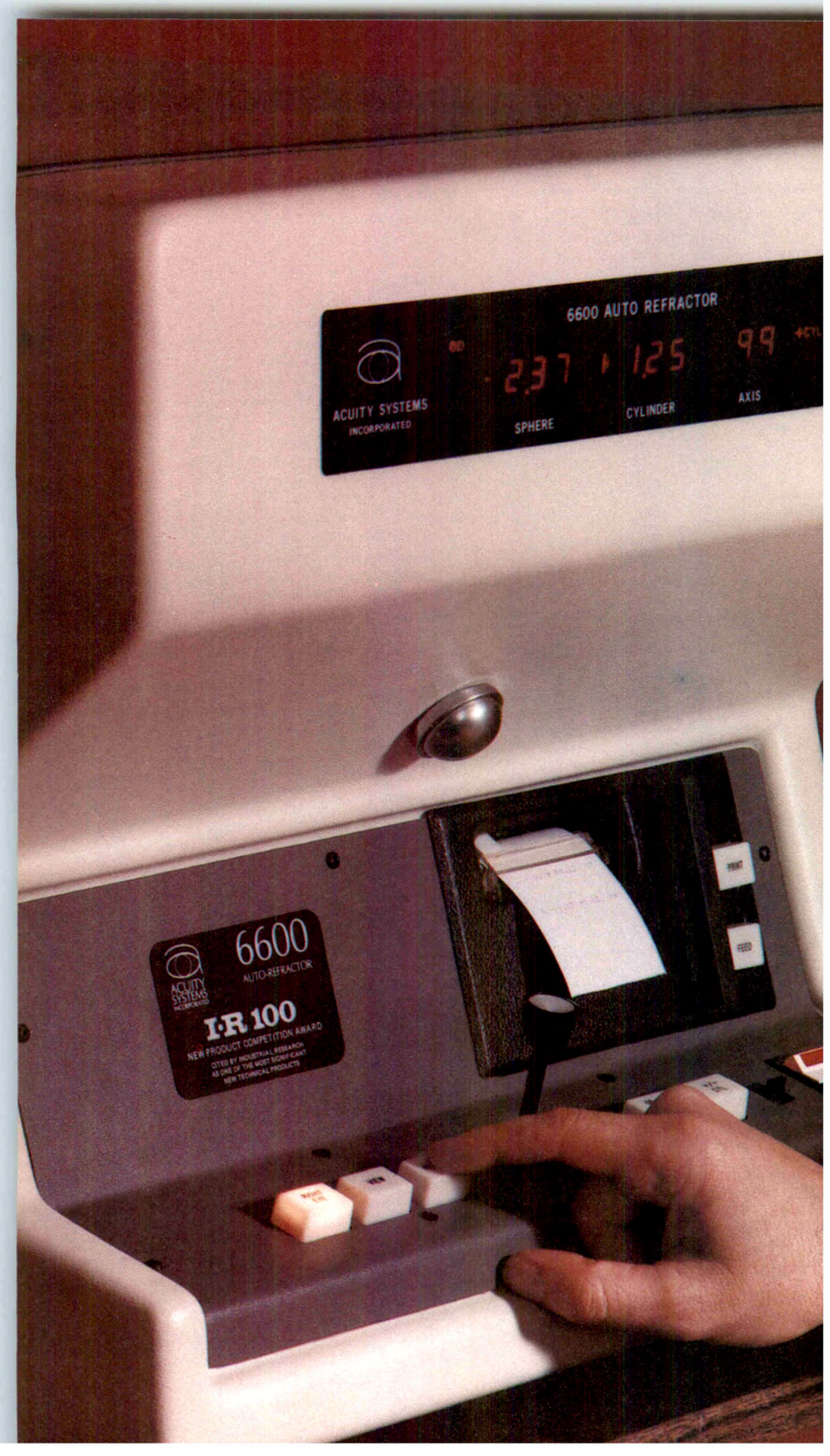
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Vehicle: Adsorbobase and Hydroxyethylcellulose

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Indications: For the control of intraocul pressure; as a miotic in the treatment of chronic, simple, open-angle glaucoma; tc counteract the effect of cycloplegics. The choice of strength should be determined the severity of the condition and the resp of the patient. To relieve tension in the tr ment of acute glaucoma Adsorbocarpine may be used alone — prior to emergency surgery — or in combination with other miotics or carbonic anhydrase inhibitors.

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Supplied: In 15 cc. sterile dropper vials — 2%, and 4% strengths.

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Precautions: Avoid overdosage.

Adverse Reactions: There are no known s effects except slight ciliary spasm with res tant temporary reduction in visual acuity. Sensitivity is infrequently observed. Cont allergy or mucosal sensitization may deve after prolonged use. If signs of sensitivity velop during treatment, or if irritation per or increases, the patient should be advise discontinue use and consult the prescribi physician.

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GUEST SPEAKERS

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Refractive Keratoplasty: Indications, Contraindictions, Complications, Results and Technics
Etiopathology of the pterygium

PERRY S. BINDER, M.D.
Corneal Graft Preservation
Corneal Anatomy, Physiology, and Wound Healing
Contact lenses and Orthokeratology

JORGE N. BUXTON, M.D.
Visual Rehabilitation
Keratoconus
Special Corneal Problems

MAX FINE, M.D.
Technics in Phakia and Pseudophakia
Corneal Regrafts
The Recurrent Pterygium:
Mucous Membrane Grafts

RICHARD TROUTMAN, M.D.
Refractive Keratoplasty in the U.S.A.
Effects of Disparate Sized Graft to Recipient Opening
Combined Keratoplasty Technics

DAN B. JONES, M.D.
Inflammatory Diseases of the Lid
Bacterial, Fungal and Visual Keratitis
Therapy of Corneal Perforation

PETER R. LAIBSON, M.D.
The Dry Eye
Herpes Simplex
Corneal Dystrophy—Anterior, Stromal, and Endothelial

ANTHONY B. NESBURN, M.D.
Herpes Simplex and Its Therapy
Recurrent Herpes: Etiology and Pathology
Permanent Wear Contacts

DAVID PATON, M.D.
Penetrating Keratoplasty—Indications, Technics
Contact Lenses and Keratoplasty
Eccentric Tectonic Lamellar Grafts

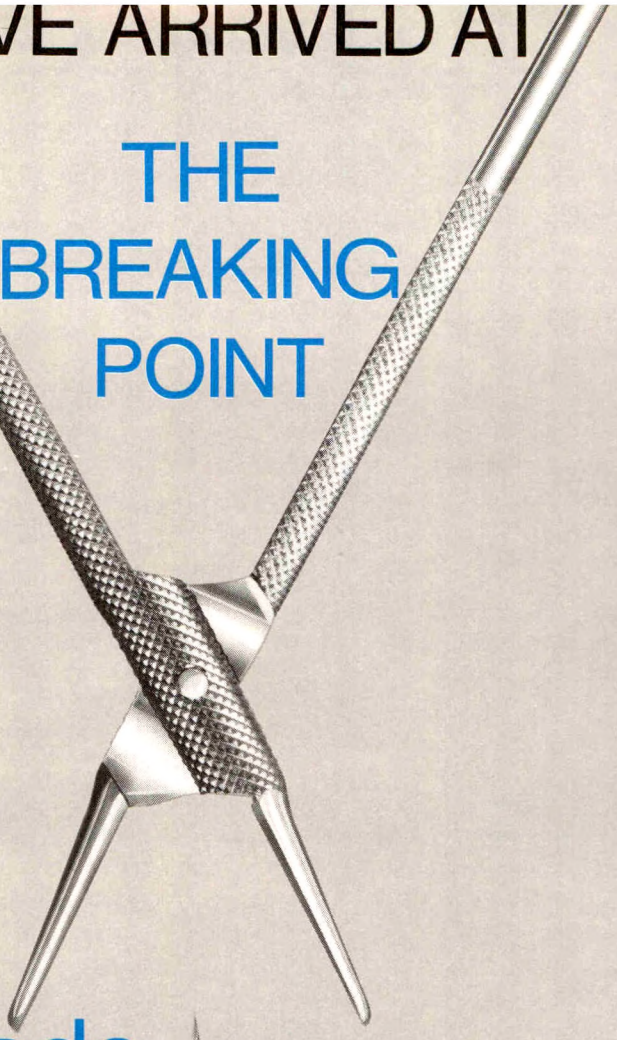
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CLINICAL APPLICATIONS OF NEW DIAGNOSTIC PROCEDURES

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PURPOSE

The multitude of new ophthalmological diagnostic tests now available is a source of great confusion to many practitioners. The goal of this program is to present a meeting which will explain these tests as simply as possible and suggest a logical approach to their utilization.

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Lorenz Zimmerman, M.D., Washington, D.C.

TOPICS

Presurgical Evaluation of Eyes with Cataracts and Other Opaque Media: ultrasonography, bright-flash electroretinography, visually evoked potential, laser interferometry, standard retinal function tests

Tumor Evaluation and Management: fluorescein angiography, ^{32}P, ultrasonography, tumor skin testing, aqueous enzymology, enucleation—pros and cons

Diagnosis and Management of Hereditary Fundus Disease: electroretinography, electro-oculography, dark adaptation, visually evoked potential, fluorescein angiography, genetic counseling, metabolic concepts

PROGRAM DIRECTORS

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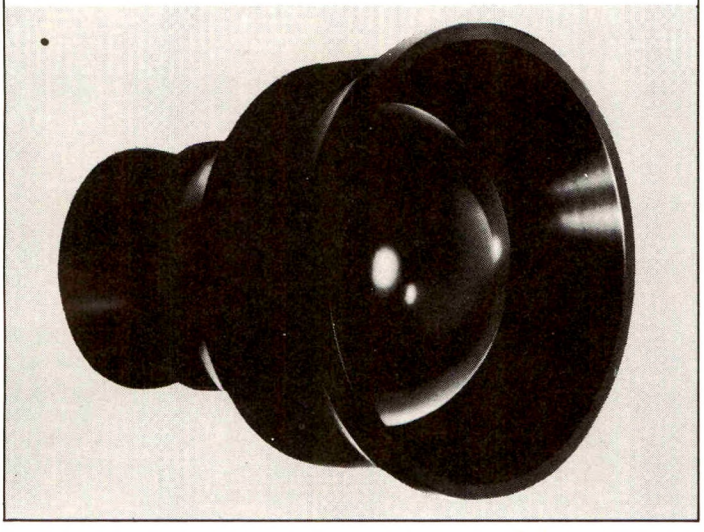
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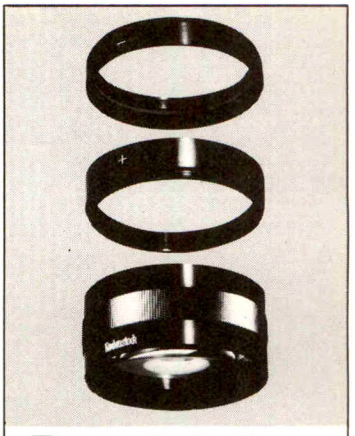
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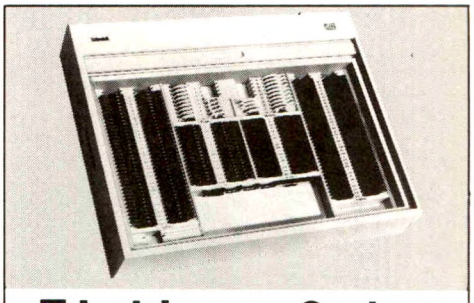
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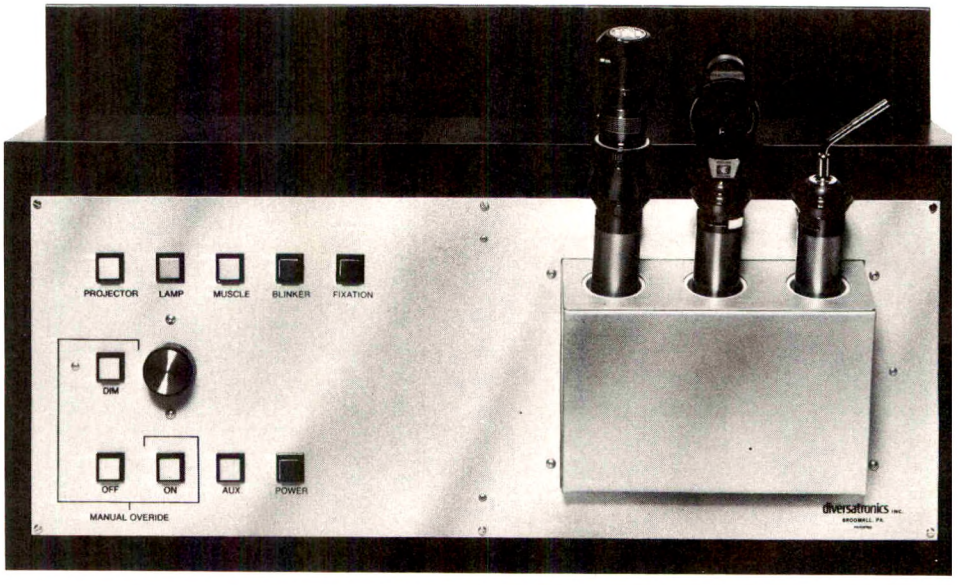
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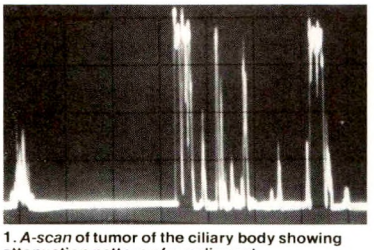
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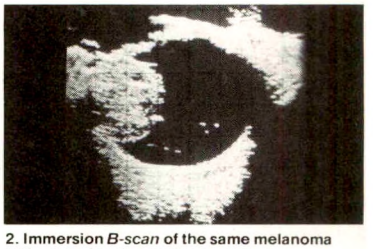
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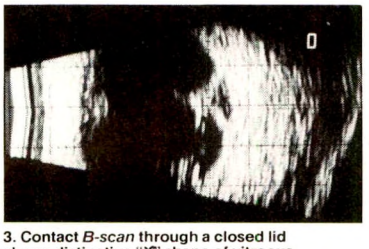
The Coleman Ophthalmoscan provides accurate measurement and diagnosis five separate ways.



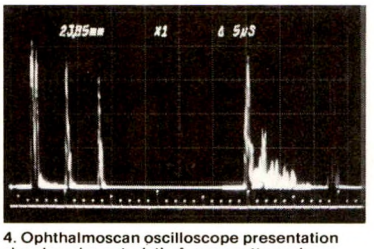
1. *A-scan* of tumor of the ciliary body showing attenuation pattern of a malignant melanoma.



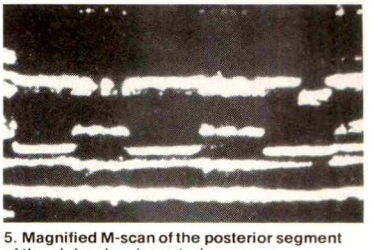
2. Immersion *B-scan* of the same melanoma with posterior vitreous hemorrhage.



3. Contact *B-scan* through a closed lid shows distinctive "X" shape of vitreous membranes and traction retinal detachment in diabetic retinopathy.

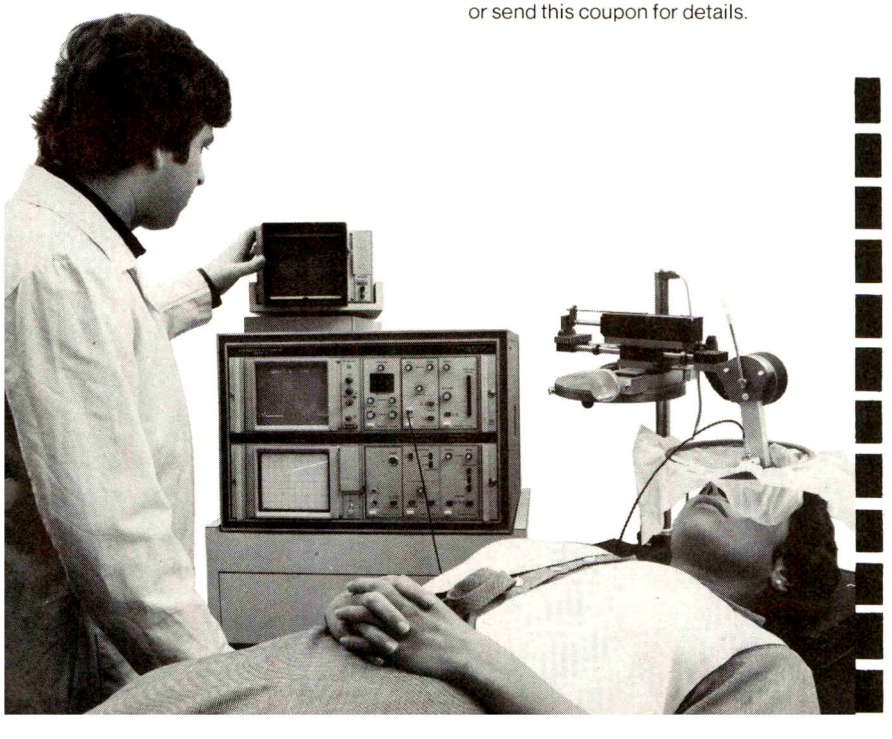


4. Ophthalmoscan oscilloscope presentation showing characteristic A-scan pattern along the visual axis and simultaneous readout of axial length in millimeters.



5. Magnified M-scan of the posterior segment of the globe showing arterio-venous pulsations.

Optimum accuracy and thoroughness in ocular and orbital diagnoses are guaranteed with the Coleman Ophthalmoscan, the world's most sophisticated ultrasonic diagnostic instrument for ophthalmology. It takes only minutes to complete an ocular and orbital examination. Simultaneous A-scan and B-scan images are augmented by M-scan; Real-Time, contact B-scan; and biometric displays. Patient preparation is minimal, requiring a simple water bath to maximize image quality. Photographic documentation is simple and instant. Call Sonometrics collect (212) 765-8205, or send this coupon for details.



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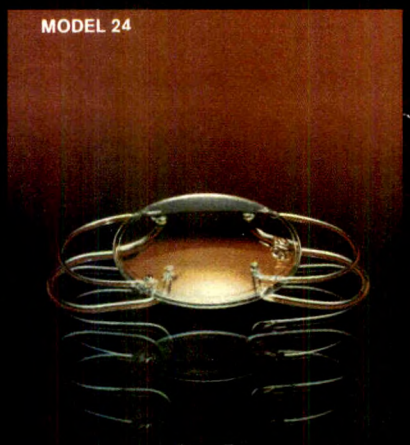
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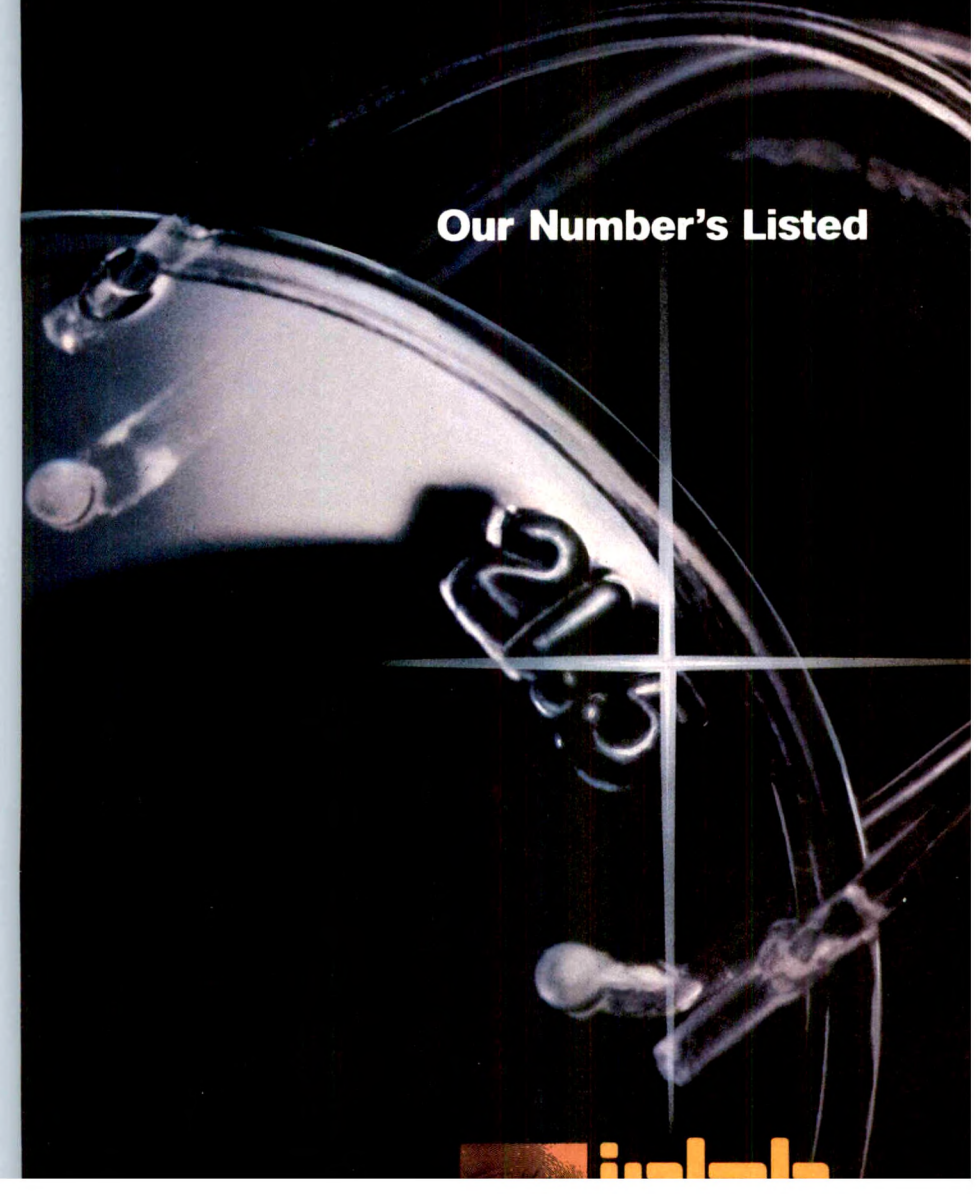
Iolab has established criteria on resolution, back focal length, and the proper identification of diopter power.



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OCULOPLASTIC SURGICAL DISSECTION COURSE

(40 HRS. CME & CAT I)

November 1-4, 1978

OBJECTIVES:
An in-depth symposium to provide the practicing and resident surgeon with an Oculoplastic Course featuring LIVE SURGERY VIDEO TAPES, FILMS, LECTURES AND PARTICIPANT'S CADAVER SURGERY.

FACULTY:

I. Baras, M. D.	P. Guibor, M. D.
L. Bergmann, M. D.	S. Hecht, M. D.
B. Cosman, M. D.	L. Herman, PhD.
N. Cousins, Esq.	A. Messina, M. D.
M. Dunn, M. D.	C. Mullenix, M. D.
D. Gaffin, Esq.	H. Settles, PhD.
H. Gould, M. D.	D. Wolfley, M. D.
M. Guibor, C. O.	and others.

SUBJECTS:
Cosmetic Blepharoplasty, Blepharoptosis, Trauma Surgery, Lid Reconstruction, Lacrimal Surgery, Orbital Reconstruction, Entropion, Ectropion, Orbital Fractures and Orbital Tumors.

OCULOPLASTIC REGISTRATION FORM
Registration $500

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Specialty: Ophth—ENT—Plastic—Derm
(circle one)

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OCULOPLASTIC COURSE

VII NERVE SURGICAL DISSECTION COURSE

(25 HRS. CME & CAT I)

October 29-31, 1978

OBJECTIVES:
A unique and practical surgical course, presented by multiple disciplines, covering the management of FACIAL PALSY and FACIAL SPASM, featuring PARTICIPANT'S CADAVER SURGERY.

FACULTY:

L. Bergmann, M. D.	M. May, M. D.
J. Conley, M. D.	S. Parisier, M. D.
M. Dunn, M. D.	H. Settles, PhD.
F. Gillen, M. D.	J. Smith, M. D.
P. Guibor, M. D.	D. Wolfley, M. D.
P. Janetta, M. D.	D. Zorub, M. D.

SUBJECTS:
Facial Nerve Testing, Dynamic-Static Techniques, Lid Spring, Silicone Encircling, Facial Reconstruction, Direct Nerve Repair and Grafting, 12-7 Hook-up Animation, Neuromuscular Pedicle Transfer and Nerve Avulsion.

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Registration $400

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Specialty: Ophth—ENT—Plastic—
Neurosurgery
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VII NERVE COURSE

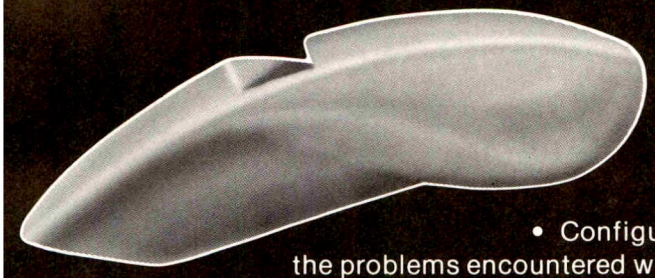
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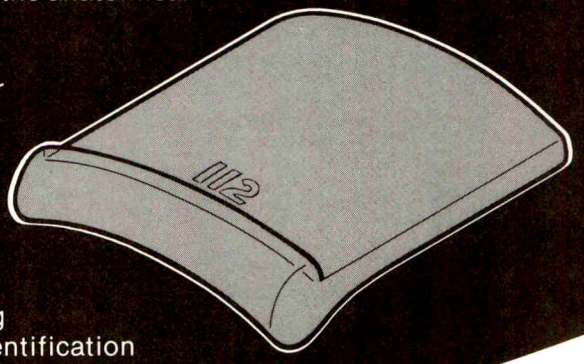


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* The Fishmouth Phenomenon II. Wedge Scleral Buckling, Arch. Ophthalmol. Vol. 95: 1782-1787, Oct. 1977.

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Turgut Hamdi, M.D.
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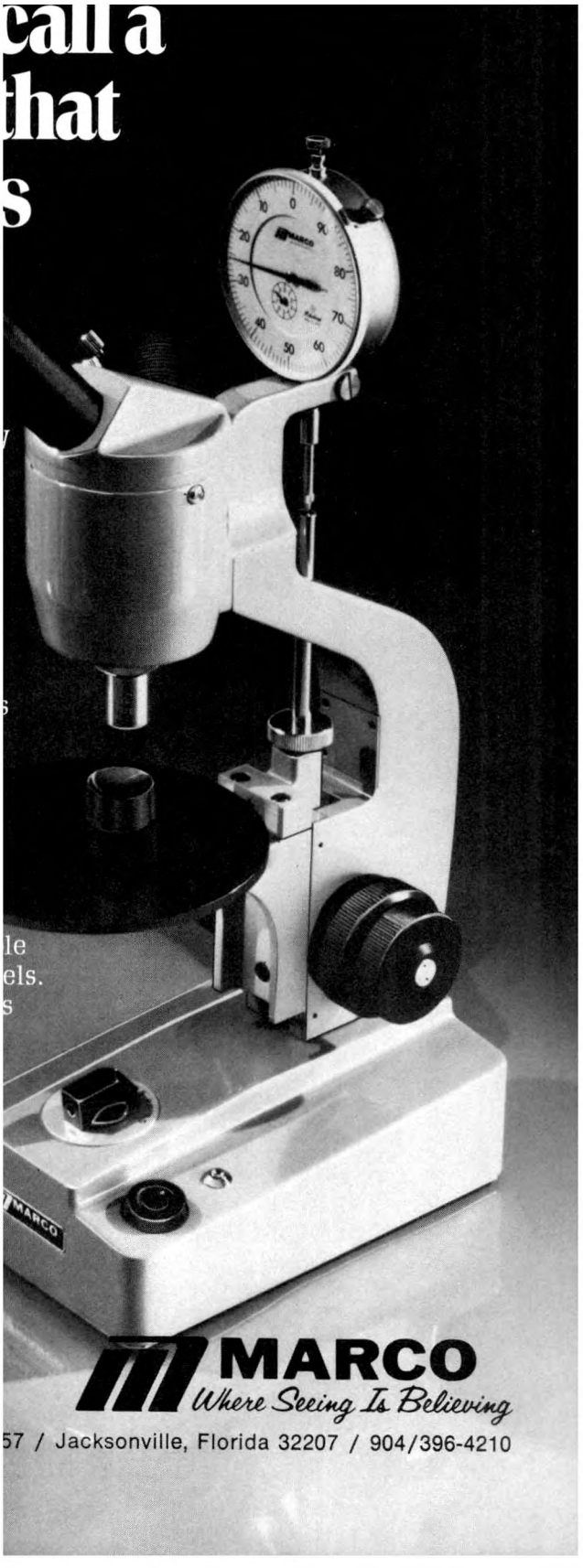
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REGISTRATION INFORMATION

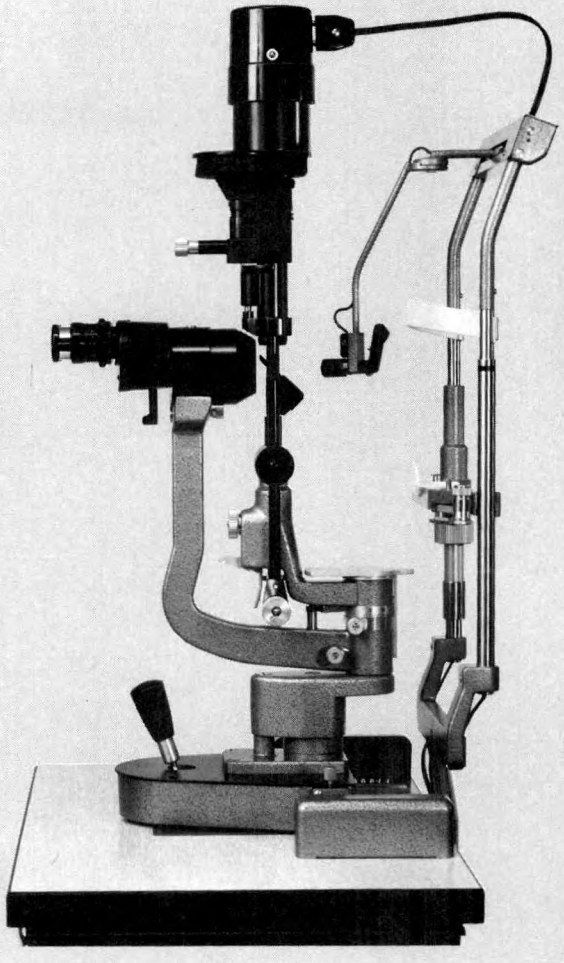
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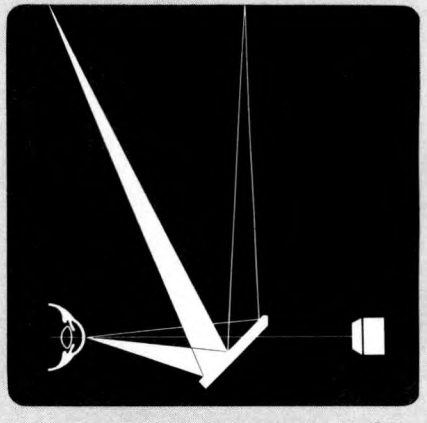
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ANNUAL CLINICAL UPDATE

Eastern Regional Meeting – Contact Lens Association of Ophthalmologists , Inc.

TWO CONSECUTIVE EDUCATIONAL MEETINGS

Wednesday, Thursday & Friday — *November 1, 2, & 3, 1978*
Saturday — *November 4, 1978*

Robert A. D'Amico, M.D.
Director, Department of Ophthalmology

G. Peter Halberg, M.D.
Meeting Coordinator

COMPLICATIONS OF CATARACT AND OTHER INTRAOCULAR SURGERY

Wednesday, November 1

GLAUCOMA • CONTACT LENS
G. Peter Halberg, M.D., Chairman

Thursday, November 2

CORNEA
Robert A. D'Amico, M.D., Chairman

INTRAOCULAR LENS
Richard D. Binkhorst, M.D., Chairman

Friday, November 3

RETINA • VITREOUS
Charles L. Schepens, M.D., Chairman
Ruth Stoddard Long, M.D., Program Chairman

REGISTRATION (Complications of Surgery)
$240.00 (includes luncheon and a social function)
$140.00 for Residents

21 Continuing Medical Education Credits, AMA Category I

SOFT CONTACT LENS UPDATE

Saturday, November 4. This *intensive,* practical "Hands On" course will be under the direction of G. Peter Halberg, M.D., with the cooperation of the distinguished faculty and the major soft contact lens manufacturers.

REGISTRATION (Soft Lens Update) $140.00 (includes luncheon)

7 Continuing Medical Education Credits, AMA Category I

FACULTY

John J. Alpar, M.D.
Joseph A. Baldone, M.D.
Richard D. Binkhorst, M.D.
Jorge N. Buxton, M.D.
Mary Bruch
Delmar R. Caldwell, M.D.
Dean Clements
Oliver H. Dabezies, Jr., M.D.
Robert A. D'Amico, M.D.
C. Richard Elander, M.D.
R. Linsy Farris, M.D.
Gerald L. Feldman, Ph.D.
John R. Finlay, M.D.
William S. Hagler, M.D.
Cary D. Hailey, Esq.
G. Peter Halberg, M.D.
Hikaru Hamano, M.D.
Jack Hartstein, M.D.
Jonathan Herschler, M.D.
Paul R. Honan, M.D.
Ronald P. Jensen, M.D.
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Irving Katz, M.D.
Richard H. Keates, M.D.
James J. Koverman
Harvey A. Lincoff, M.D.
Ruth Stoddard Long, M.D.
Donald L. MacKeen, Ph.D
Francis Manapoli, M.D.
Leroy G. Meshel, M.D.
Kiran Randeri, Ph.D.
Charles D. J. Regan, M.D.
Morton L. Rosenthal, M.D.
H. Roth, M.D.
Arnauld F. Scafidi, M.D.
Charles L. Schepens, M.D.
Murray Sibley, Ph.D.
John Szabocsik, Ph.D.
Max Talbott, Ph.D.
William M. Townsend, M.D.
Richard C. Troutman, M.D.
Ernst van Beuningen, M.D.
Wichard A. J. van Heuven, M.D.
Thom Zimmerman, M.D.

Support by the following firms is gratefully acknowledged: Soft Lenses, Inc. - Hydrocurve™ • Bausch & Lomb - Soflens Allergan Pharmaceuticals, Burton, Parsons & Company, Inc. • American Optical Company - AO Soft • Synemed - Fieldmaster Barnes-Hind Pharmaceuticals, Inc. • National Patent Development Corporation-Hydron

For registration or information for either or both meetings, contact:

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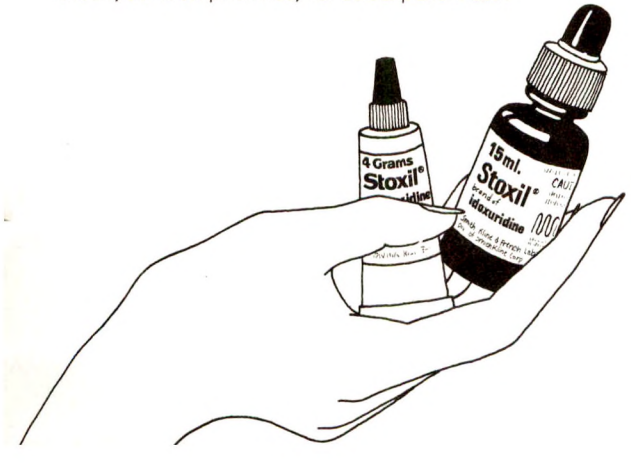
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Check your local pharmacy for actual patient cost.



Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indication: Herpes simplex keratitis (topical use only).

Contraindications: Known or suspected hypersensitivity to any of the components.

Warning: Administer with caution in pregnancy or women of childbearing potential. Malformations were reported in one study in rabbits when idoxuridine was instilled in the eyes of the dams; a subsequent, more detailed study in rabbits showed no such effects, even at substantially higher dosages.

Precautions: If there is no response in epithelial infections after 7 or 8 days, other therapy should be considered. Recommended frequency and duration of administration should not be exceeded. Not effective in corneal inflammations if herpes simplex is not present. Boric acid should not be used concomitantly. To insure stability is maintained, the solution should not be mixed with other medications.

Adverse reactions: Occasionally, irritation, pain, pruritus, inflammation, or edema of the eye or lid; rarely, allergic reactions have been reported. Photophobia has occurred. Occasionally, small punctate defects (which may be a manifestation of the infection), corneal clouding, and stippling of the corneal epithelium have been observed.

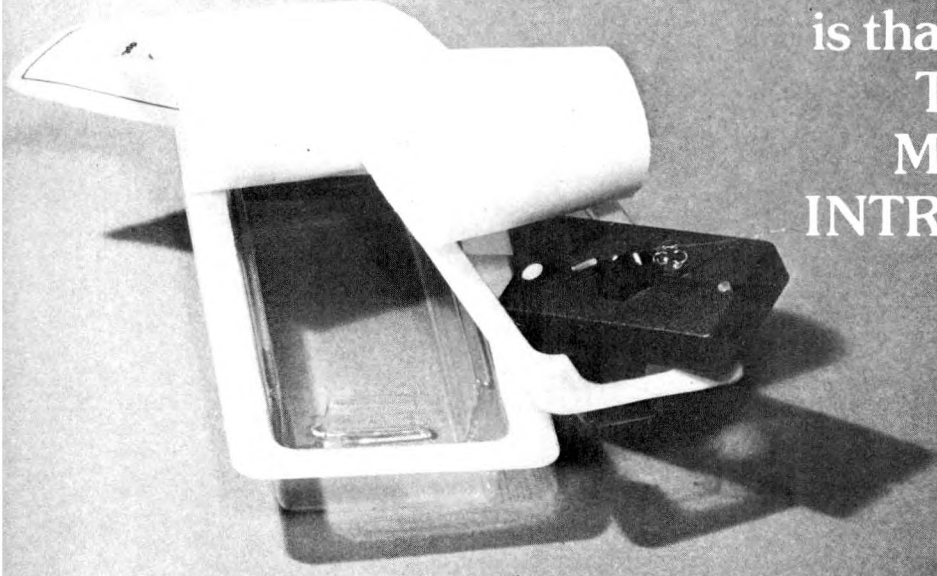
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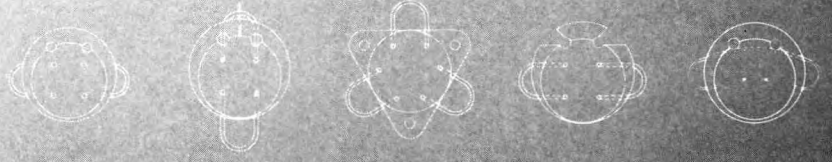
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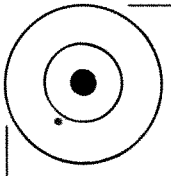




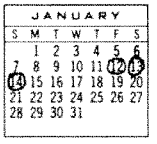
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MID-WINTER NATIONAL MEETING

CONTACT LENS ASSOCIATION OF OPHTHALMOLOGISTS

January 12-14, 1979 • Sahara Hotel, Las Vegas, Nevada

16 Hours CME Credits—AMA Category I

DISTINGUISHED VISITING LECTURER
Jose I. Barraquer, M.D.
Present Status of Keratophakia for the Correction of Hyperopia and Aphakia

ELEVENTH CONRAD BERENS LECTURE
Jorge N. Buxton, M.D.
Post Surgical Visual Rehabilitation

THIRD ANNUAL THEODORE E. OBRIG MEMORIAL LECTURE
Mr. Jack Moore
A Practical Approach for the Average Clinical Practice

PRACTICE MANAGEMENT SEMINAR Herschell H. Boyd, M.D., Chairman

Immediately preceding the Mid-Winter National Meeting, there will be an all day Ophthalmic Practice Management Seminar on Thursday, January 11, 1979. No additional registration fee for the Pract Management Seminar.

Friday, January 12

CONTACT LENS PRESENTATIONS (Free Papers)
Jack Hartstein, M.D., Presiding

Symposium: INDUSTRIAL SAFETY AND CONTACT LENSES
J. Elliott Blaydes, Jr., M.D. and
Robert J. Crossen, M.D., Co-Moderators
Joseph F. Novak, M.D., Arthur H. Keeney, M.D., and G. Peter Halberg, M.D.

Symposium: PROLONGED WEAR - UPDATE
Walter J. Stark, M.D., Moderator
Jorge Buxton, M.D., Richard H. Keates, M.D., and Anthony J. Nesburn, M.D.

Mary Bruch
Food and Drug Administration

THIRD ANNUAL THEODORE E. OBRIG MEMORIAL LECTURE
Mr. Jack Moore
A Practical Approach for the Average Clinical Practice

SPORTS AND CONTACT LENSES
Richard H. Keates, M.D.

DISTINGUISHED VISITING LECTURER

Jose I. Barraquer, M.D.

Present Status of Keratophakia for the Correction of Hyperopia and Aphakia

CONTACT LENS COURSES-Section I

(Pre-registrants may select courses by mail)

The Extended Wear of Soft Contact Lenses
Director—Perry S. Binder, M.D.
Instructors—Richard Keates, M.D. and Edward Shaw, M.D.

Management of Corneal and Contact Lens Problems
Director—Robert A. D'Amico, M.D.
Instructors—Joseph A. Baldone, M.D. and John F. Morgan, M.D.

How to Select the Best Soft Lens for Your Patient
Director—Ellis Gruber, M.D.

Management of the Contact Lens Problem Case
Director—G. Peter Halberg, M.D.

Soft and Hard Contact Lens Fitting with Custom Design Lenses
Director—Herschell H. Boyd, M.D.
Instructor—Paul R. Honan, M.D.

Fitting of Oxygen Permeable Contact Lenses
Director—Jay Lippman, M.D.

Review of Hard & Soft Lens Technology
Director—Joseph W. Soper
Instructors—Kenneth W. Swanson, Frank B. Sanning, Ralph T. Sutton, and Jack W. Moore

Therapeutics & Cosmetic Scleral Contact Lenses
Director—Herbert L. Gould, M.D.
Instructors—John W. Espy, M.D. and Leroy G. Meshel, M.D.

Contact Lens Fitting in Infants and Children
Director—Harold P. Koller, M.D.
Instructors—Anthony Caputo, M.D., Jerry Maida, M.D., and J. Matthew Robinoweiz, M.D.

Modification of Hard Contact Lenses
Director—Marvin A. Garland, M.D.
Instructors—Paul Honan, M.D. and Vic Brown

CONTACT LENS COURSES-Section II

(Pre-registrants may select courses by mail)

Utilization and Training of a Contact Lens Technician
Director—Robert J. Crossen, M.D.

Therapeutic Uses of Soft Contact Lenses
Director—Edward Shaw, M.D.
Instructors—Frederick Brightbill, M.D., Walter Stark, M.D., and Robert G. Webster, M.D.

The Aquaflex Hydrophilic Lens - Review of Vault Theroy of Fitting, Research & Clinical Experience
Director—Ellis Gruber, M.D.

Keratoconus
Director—Frank B. Hoefle, M.D.
Instructors—Richard G. Lembach, M.D., Jorge N. Buxton, M.D., James Koverman, and Delmar R. Caldwell, M.D.

Specialized Techniques of Lens Fitting
Director—Joseph W. Soper
Instructors—James C. Tannehill, Vernon R. Lamb, and William McGuire

Bifocal & Multifocal Contact Lenses for the Presbyope & Aphake
Directors—Abraham Schlossman, M.D., and Frank J. Weinstock, M.D.
Instructors—George Jones, M.D., George Pugh, M.D., Carolyn Schlossman, Norman Schmid, Sr., Charles E. Clevenger, M.D., Ronald Akashi, M.D., and Kenneth Michaile, M.E.

Clinical Aspects of Fitting the Hydrocurve Lens
Director—James S. Russell, M.D.
Instructor—Gerald Feldman, Ph.D.

Extended Contact Lens Wear
Director—Anthony B. Nesburn, M.D.
Instructors—Dwight H. Cavanagh, M.D., Steven Kelly, M.D., and Roger Langston, M.D.

Astigmatism Correction with Hard & Soft Contact Lenses
Director—Paul Honan, M.D.
Instructors—Whitney Sampson, M.D.

Hydrogel Lathe Lenses Versus Spin Cast Lenses
Director—Chester J. Black, M.D.

Saturday, January 13

INTRAOCULAR LENS PRESENTATIONS (Free Papers)

Jorge N. Buxton, M.D., Presiding

Symposium: THE CONTACT LENS CORRECTION OF ASTIGMATISM

Joseph A. Baldone, M.D., Moderator

Participants: James Tannehill, Whitney G. Sampson, M.D., Philippe Baronet, M.D., and Harold Stein, M.D.

Symposium: ASTIGMATISM - SURGICAL CORRECTION

Herbert E. Kaufman, M.D., Moderator

The Practical Application of Keratomileusis and Keratophakia ..... Miles Friedlander, M.D.

New Approaches to the Management of Refractive Errors ..... Randall Olson, M.D.

Other Participants to be Announced

THE FUTURE WAS YESTERDAY

Lawrence A. Winograd, M.D.

ELEVENTH CONRAD BERENS LECTURE
Jorge N. Buxton, M.D.
Post Surgical Visual Rehabilitation

Symposium: PITFALLS IN LENS IMPLANTATION
Harold A. Stein, M.D., Moderator

Errors in Patient Selection ..... Harold A. Stein, M.D.
Pitfalls at the Time of Surgery ..... Richard Kratz, M.D.
Pitfalls in the Immediate Post-op Period ..... Marvin Kwitko, M.D.
Pitfalls in the Late Post-op Period ..... Herve Byron, M.D.
Guiding the Resident in Lens Implantation ..... Leeds Katzin, M.D.
Question and Answer Period

Symposium: SURGICAL KERATOMETRY
Herbert E. Kaufman, M.D., Moderator
Participants to be Announced

Symposium: SURGICAL TECHNIQUES FOR VARIOUS IMPLANTS (Movies)
Jack Hartstein, M.D., Moderator

Technique with the Copeland Lens ..... Ned Snyder, M.D.
Technique with the Copeland Lens ..... William U. McReynolds, M.D.
Medallion Lens in Association with Intracapsular Cataract Extraction ... Manus C. Kraff, M.D.
2-Loop Binkhorst Lens ..... Richard Kratz, M.D.
4-Loop Binkhorst Lens ..... Henry Hirschman, M.D.
Federov Sputnik Lens and the Platinum Clip Lens ..... Marvin L. Kwitko, M.D.
Primary Implants of the Choyce Lens ..... Jerald L. Tennant, M.D.
Secondary Implantation of the Azar Tripod ..... Robert Azar, M.M.D.
Shearing Lens ..... Steven P. Shearing, M.D.
Suturing Techniques ..... C. William Simcoe, M.D.
Panel Discussion

Sunday, January 14

Symposium: INSTRUMENTS FOR INTRAOCULAR LENS SURGERY
Robert F. Azar, M.D., Moderator
Participants: John Sheets, M.D. and Henry Hirschman, M.D.

Symposium: COMPLICATIONS ASSOCIATED WITH VARIOUS INTRAOCULAR LENSES
Richard P. Kratz, M.D., Moderator
Other Participants to be Announced

Symposium: INTRAOCULAR LENS REMOVAL
Henry Hirschman, M.D., Moderator
Other Participants to be Announced

Sunday, January 14 Continued

Symposium: SECONDARY LENS IMPLANTATION
Jerald L. Tennant, M.D., Moderator
Other Participants to be Announced

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CLAO Annual Business Meeting will be held on Friday, January 12, 1979.

Wine Tasting Party (Friday, January 12) - Sponsored by Barnes-Hind Pharmaceuticals

International Party (Saturday, January 13) - Sponsored by Burton, Parsons & Co.

Oliver H. Dabezies, Jr., M.D.	G. Peter Halberg, M.D., F.A.C.S.	Jack Hartstein, M.D.
Chairman, Mid-Winter Meeting	*Secretary of Meeting*	*President, CLAO*

BASIC COURSE-OPHTHALMIC ASSISTANTS
Saturday, January 13
2:00 p.m.-5:30 p.m.
Harold A. Stein, M.D., Program Director
Bernard J. Slatt, M.D., Assistant Program Director
Ms Penny Cook and Mrs. Maija Kaufman, Program Coordinators

Terminology
Anatomy of the Cornea
Practical Corneal Physiology
Clinical Selection and Evaluation of Patients
Taking Patient Measurements
Evaluating Lens Parameters
Care and Handling of Soft Lenses
Insertion and Removal Techniques
Selecting the Right Lens
Assessing the Fit
Soft Lens Problems and Solutions
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Office Practice Management

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PRE-REGISTRATION – CLAO MID-WINTER NATIONAL MEETING

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Immediately preceding the scientific session, an optional Practice Management Seminar will be conducted on Thursday, January 11, 1979. There is no registration fee for the Practice Management Seminar. The registration fee for the Scientific Session is the total fee for all sessions.

Registration for the Scientific Session will take place on Wednesday, January 10 from 6:00 p.m. to 8:30 p.m. and Thursday, January 11 from 8:00 a.m. to 5:30 p.m.

☐ Physician Member of CLAO ($200.00)

☐ Physician Non-Member ($250.00)

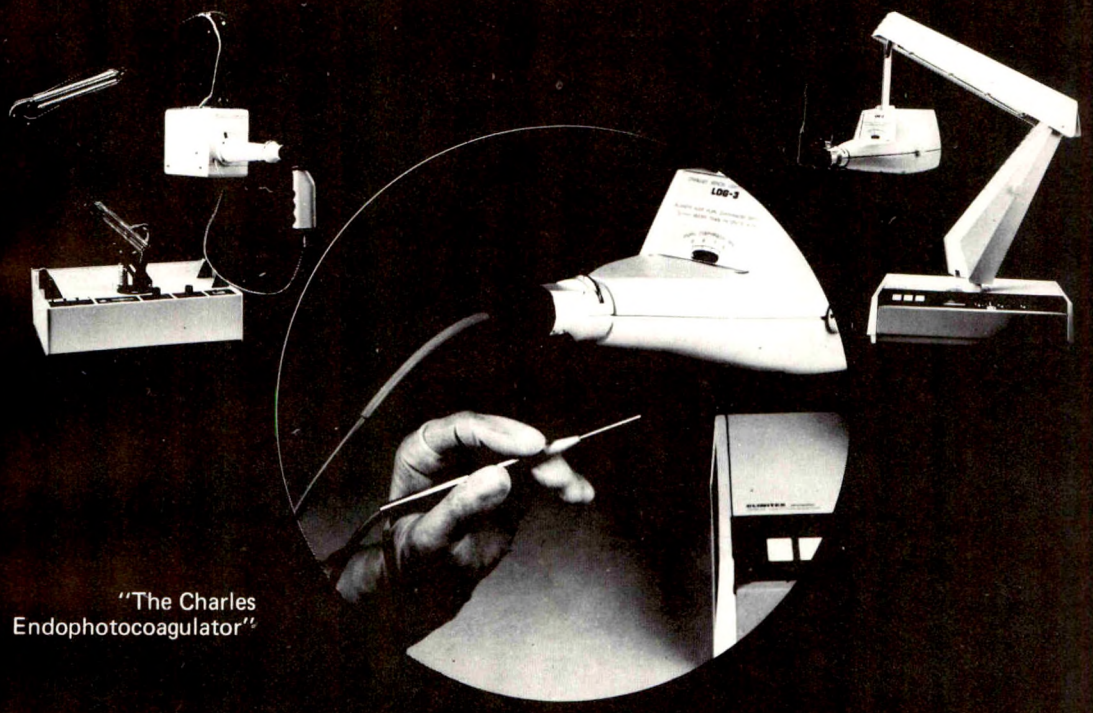
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☐ All Other ($275.00)

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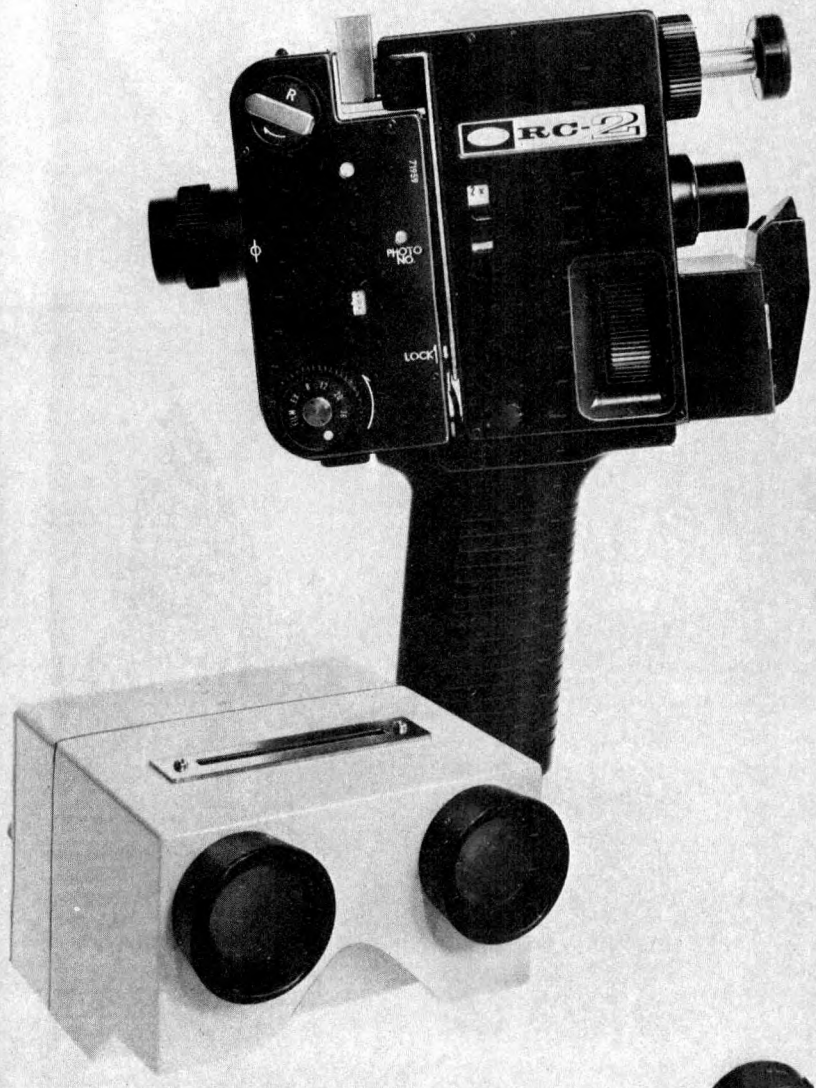
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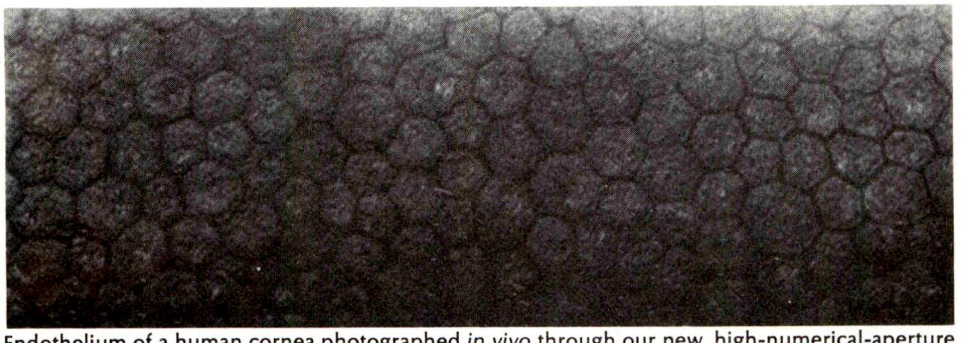
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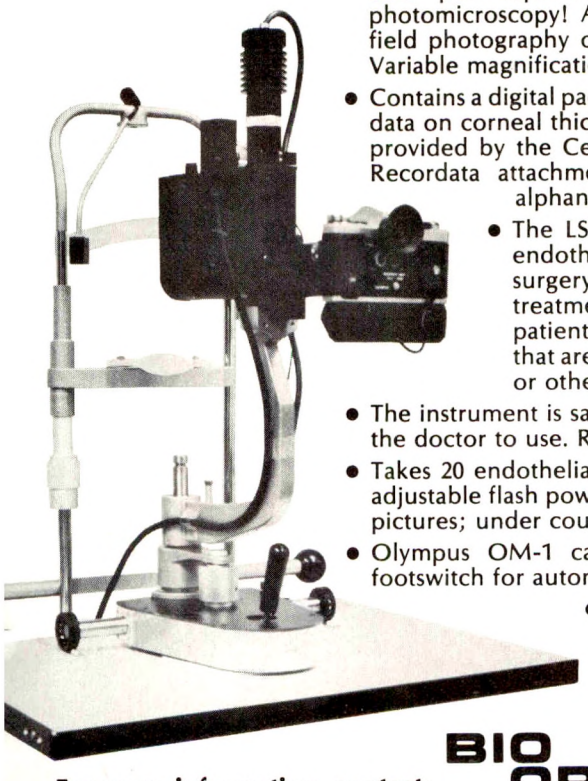
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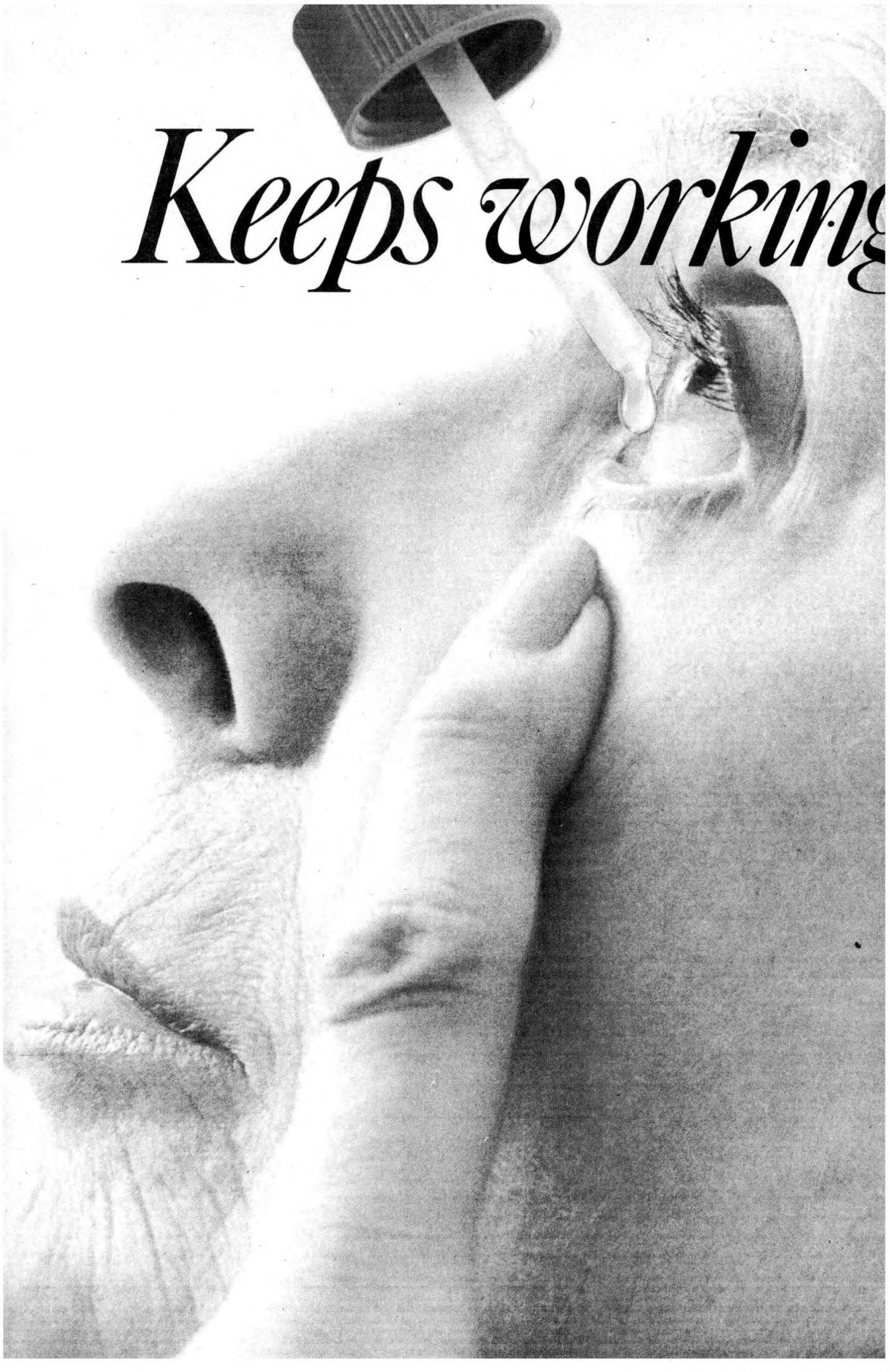
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See next page for prescribing information.



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in the management of chronic simple glaucoma or glaucoma secondary to aphakia

BRIEF SUMMARY
(For full prescribing information, see package circular.)
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PHOSPHOLINE IODIDE is a long-acting cholinesterase inhibitor for topical use.

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Accommodative esotropia—Concomitant esotropias with a significant accommodative component.

Contraindications: 1. Active uveal inflammation.

2. Most cases of angle-closure glaucoma, due to the possibility of increasing angle block.

3. Hypersensitivity to the active or inactive ingredients.

Warnings: 1. *Use in Pregnancy.* Safe use of anticholinesterase medications during pregnancy has not been established, nor has the absence of adverse effects on the fetus or on the respiration of the neonate.

2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patients receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.

3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same time undergoing treatment with systemic anticholinesterase medications for myasthenia gravis, because of possible adverse additive effects.

Precautions: 1. Gonioscopy is recommended prior to initiation of therapy.

2. Where there is a quiescent uveitis or a history of this condition, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.

3. While systemic effects are infrequent, proper use of the drug requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into the nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.

4. Temporary discontinuance of medication is necessary if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregularities occur.

5. Patients receiving PHOSPHOLINE IODIDE who are exposed to carbamate or organophosphate type insecticides and pesticides (professional gardeners, farmers, workers in plants manufacturing or formulating such products, etc.) should be warned of the additive systemic effects possible from absorption of the pesticide through the respiratory tract or skin. During periods of exposure to such pesticides, the wearing of respiratory masks, and frequent washing and clothing changes may be advisable.

6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects.

7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.

8. PHOSPHOLINE IODIDE (echothiophate iodide) should be used with great caution, if at all, where there is a prior history of retinal detachment.

Adverse Reactions: 1. Although the relationship, if any, of retinal detachment to the administration of PHOSPHOLINE IODIDE has not been established, retinal detachment has been reported in a few cases during the use of PHOSPHOLINE IODIDE in adult patients without a previous history of this disorder.

2. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.

3. Activation of latent iritis or uveitis may occur.

4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.

5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.

6. Lens opacities occurring in patients under treatment for glaucoma with PHOSPHOLINE IODIDE have been reported and similar changes have been produced experimentally in normal monkeys. Routine examinations should accompany clinical use of the drug.

7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.

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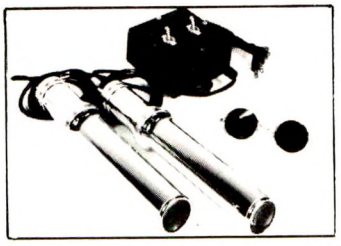
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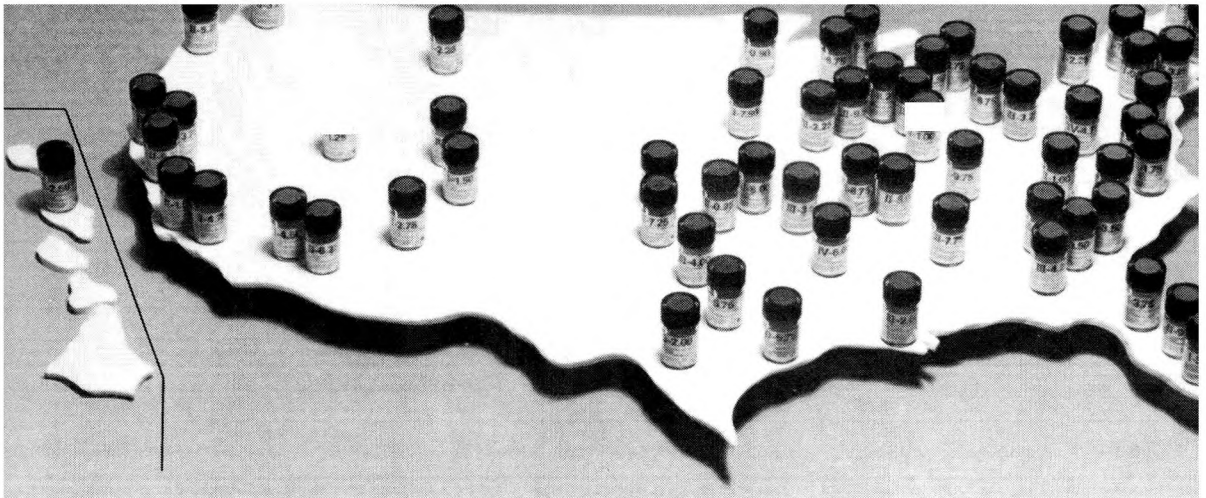
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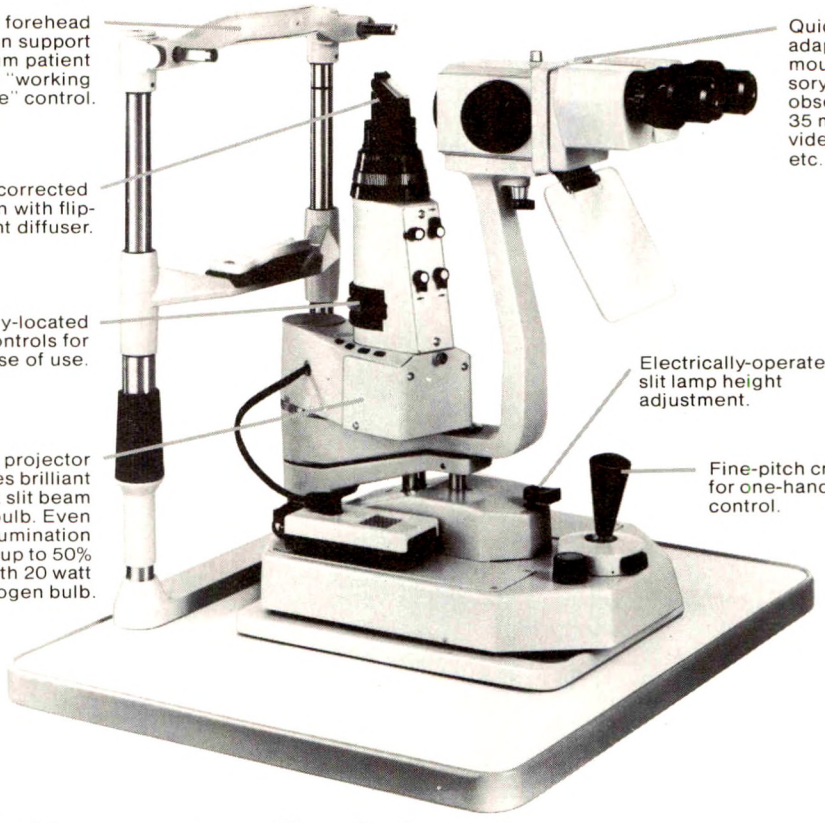


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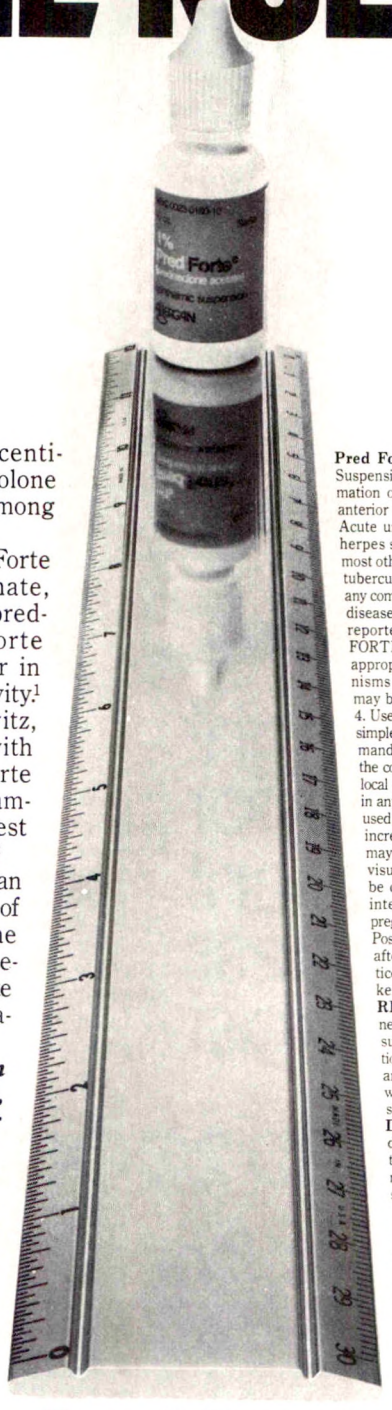
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REFERENCE NOTES: 1. Leibowitz, H. M. and Kupferman, A. Bioavailability and therapeutic effectiveness of topically administered corticosteroids. Trans Am Acad Ophthalmol Otolaryngol 79 (1): op 78-op 88, 1975. 2. Ibid. 3. Ibid.

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AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 86 NUMBER 4 OCTOBER, 1978

NEOVASCULOGENIC ABILITY OF PROSTAGLANDINS, GROWTH FACTORS, AND SYNTHETIC CHEMOATTRACTANTS

DAVID BENEZRA, M.D.

Bethesda, Maryland

The mechanism of blood vessel proliferation during the normal embryogenesis and in diseases of the eye has attracted many ophthalmologic researchers.[1-5] But, since Michaelson's[1,6] original articles regarding the presence of a neovascular factor (x-factor), little progress has been made in the characterization or isolation of the mechanism. In retrolental fibroplasia the direct influence of oxygen on the retinal vessels has been demonstrated.[7,8] However, the oxygen theory fails to explain all the clinical and experimental phenomena observed during the neovascular process. The isolation of an angiogenic substance from growing tumor cells, a tumor angiogenic factor,[9] and the demonstration of a neovascular attracting factor produced by activated blood leukocytes[10,11] renewed the interest in Michaelson's x-factor.

In previous reports, I[10,11] suggested that neovasculogenesis might be a basic phenomenon activated by various stimuli such as oxygen in retrolental fibroplasia, metabolic changes in diabetes, products of inflammatory reactions, a tumor angiogenic factor in growing solid tumors, a neovascular attracting factor in immunological reactions. More recently, I have observed the neovasculogenic ability of prostaglandins of the E series and suggested that these might be the active compounds in tumor angiogenic and neovascular attracting factors. I describe herein the role of various groups of prostaglandins in neovasculogenesis and the possible involvement of growth factors and synthetic chemoattractants in the induction of new vessel growth.

MATERIAL AND METHODS

The neovascular attracting ability was evaluated by incorporating the tested material into ethylene-vinyl-acetate copolymer (40% vinyl-acetate by weight), Elvax 40. Under aseptic conditions, 50 or 100 μl of a 10% casting solution of Elvax 40 in methylene chloride was mixed with the dry substance to be tested. The methylene was allowed to evaporate from the mixture under a laminar flow hood. The resulting film of polymer was cut into 1-mm^2 pieces, which were used as implants. Approximately 20 implants were obtained from each preparation. Each implant sequestered a 1.0- to 20-μg substance to be tested according to the initial amount used for the preparation of the implants.

Under the operating microscope, an incision of half the depth of the corneal thickness and 4 mm wide was made at the center of the cornea. Radial midstromal tunnels toward the corneoscleral limbus were formed with a thin cyclodialysis

From the Clinical Branch, National Eye Institute, National Institutes of Health, Bethesda, Maryland.

Reprint requests to David BenEzra, M.D., Department of Ophthalmology, Hadassah Hebrew University Hospital and Medical School, Hadassah Ein Karem, Jerusalem, Israel.

spatula in two opposite directions. Two implants were then inserted into the tunnels and positioned 2 mm from the corneoscleral limbus at the 12 and 6 o'clock meridians. In the preliminary set of experiments, an empty implant of Elvax 40 was inserted as a control in front of each implant, sequestering the tested material in an unmasked manner. During the second phase of the experiment, the two implants in each eye were chosen at random from coded preparations. The vessel growth and proliferation was assessed under the operating microscope every 24 hours for the first two days and every two days thereafter. On the sixth day, the length of the leading vessel from corneoscleral limbus to implant and the extent of the active neovascular base at the corneoscleral limbus were recorded and the eyes were removed for histology. Implants sequestered 20 μg of the less reactive prostaglandins per implant and 1 or 5 μg of the more reactive prostoglandins per implant.

Four peptides extensively studied for their chemotactic activity in vitro[12,13] were sequestered in corneal implants (20 μg per implant) and tested for their in vivo chemoattracting and neovasculogenic ability. Two formylated peptides, formyl-methyonyl-phenylalanine and formyl-methyonyl-leucine-phenylalanine, as well as two nonformylated peptides, methyonyl-leucine and methyonyl phenylalanine, were tested in vitro. Two nanograms of fibroblast growth factor or epidermal growth factor per microculture was used to test their ability to stimulate the DNA synthesis in human and rabbit corneal keratocyte cultures. Corneal implants were prepared with 1 or 10 μg of fibroblast or epidermal growth factor. One unit of nerve growth factor per microculture was added for the in vitro stimulatory effect on DNA synthesis. Ten units were sequestered into Elvax 40 for testing in vivo neovasculogenic effect.

Human corneas were obtained at autopsy within 24 to 48 hours after death. Rabbit corneas were used within an hour after enucleation. The corneas were dissected, and pure keratocyte cultures were initiated from small stromal explants in short-term macrocultures. The metabolic activity of the outgrowing keratocytes was assayed as previously described[14,15] by using the microculture technique developed in our laboratory.

Results

The prostaglandins stimulate neovasculogenic activity (Table 1). Prostaglandin E_1 is especially neovasculogenic. All 31 implants sequestering 1 μg of PGE_1 induced a marked proliferation of corneoscleral limbal vessels. In this system, PGE_2 is a weaker neovascular stimulant than PGE_1. Whereas 27 of 28 implants of PGE_2 showed a neovascular attracting ability soon after implantation, only 20 of 28 implants sequestering 5 μg of PGE_2 per implant sustained their neovascular attracting ability on the sixth day. Prostaglandin $F_1\alpha$ demonstrated a positive neovascular response in one of 20 implants. Three of 12 implants with 20 μg of $PGF_2\alpha$ per implant attracted new vessels. Prostaglandins A_1 and D_2 in ten and 18 implants, respectively, showed no activity similar to the 84 control implants of Elvax 40. The characteristic histologic appearance of the corneas six days after implantation is illustrated (Fig. 1). Corneas with implants sequestering 1μg of PGE_1 demonstrated marked neovascularization (A) and an infiltration of polymorphonuclear and mononuclear cells. In contrast, corneas with empty implants of Elvax 40 did not show any activity (B).

Whereas the fibroblast growth factor and the epidermal growth factor were potent in stimulating DNA synthesis and proliferation of human and rabbit kerocytes in vitro, they were nonvasculogenic

TABLE 1

NEOVASCULAR MEDIATING ACTIVITY OF PROSTAGLANDINS

Compound Tested	μg Per Implant	Implants		Neovascularization		
		Total	Active	Length*	Base†	Surface‡
PGE_1	1.0	31	31	1.9 ± 0.2	7.4 ± 0.9	13.8 ± 2.6
PGE_2	5.0	28	20	0.7 ± 0.6	3.7 ± 2.5	3.8 ± 3.7
PGD_2	20.0	18	0	0.0	0.0	0.0
PGA_1	20.0	10	0	0.0	0.0	0.0
$PGF_1\alpha$	20.0	20	1	0.1 ± 0.3	0.3 ± 1.3	0.3 ± 1.3
$PGF_2\alpha$	20.0	12	3	0.3 ± 0.6	2.0 ± 3.6	2.7 ± 4.9
Elvax 40	—	84	0	0.0	0.0	0.0

*Mean length ± standard deviation (mm) of the leading vessel from corneoscleral limbus to implant.
†Mean active base of neovascularization. Represents half the extent of the corneoscleral limbal circumference demonstrating corneal invasion.
‡Mean corneal surface of neovascularization (mm^2) induced by an implant. Calculated as an approximate triangular shaped tuft of neovascularization.

in vivo in concentrations of 1 μg per implant (Table 2). Higher concentrations of growth factor induced a slight corneal edema and a small, but significant vessel proliferation from the corneoscleral limbus toward the implant. The histology of an active implant sequestering 10 μg of epidermal growth factor is demonstrated (Fig. 1, C). There was a moderate growth of new vessels and a relatively little infiltration of mononuclear cells. Noteworthy in this section also are the larger and more columnar basal epithelial cells. The epithelium is hyperplastic and thickest nearer the implant. The nerve growth factor showed only a mild stimulatory effect on the DNA synthesis of keratocyte cultures in vitro and had no neovasculogenic ability (Table 2).

The marked difference between the in vitro chemoattracting activity of formylated synthetic peptides and their activity in the cornea in vivo is illustrated (Table 3). The peptide formyl-methionyl-leucine-phenylalanine, which is a potent in vitro chemoattractant, seldom induced mild infiltration of leucocytes in vivo (Fig. 1, D). However, none of the implants sequestering the formylated peptides demonstrated any neovascular activity.

DISCUSSION

Based on previous experimental and clinical observations and the findings that activated leukocytes release a neovascular attracting factor, I suggested a basic scheme for the regulation of ocular blood vessel proliferation in normal conditions and in disease.[10,11] I postulated that common metabolites, termed "neovascular mediating substance(s)," are released after various stimuli. These substances mediate and probably also regulate the neovascular activity (Fig. 2). In an attempt to identify the neovascular mediating substances, cyclic nucleotides, prostaglandins, chemoattractants, and growth factors were assayed for their neovasculogenic ability. In previous studies, cyclic adenosine monophosphate and cyclic guanine monophosphate did not stimulate neovascularization (unpublished data). The data in this study strongly support the possibility that the role of neovascular mediating substance is fulfilled by prostaglandins of the E series.

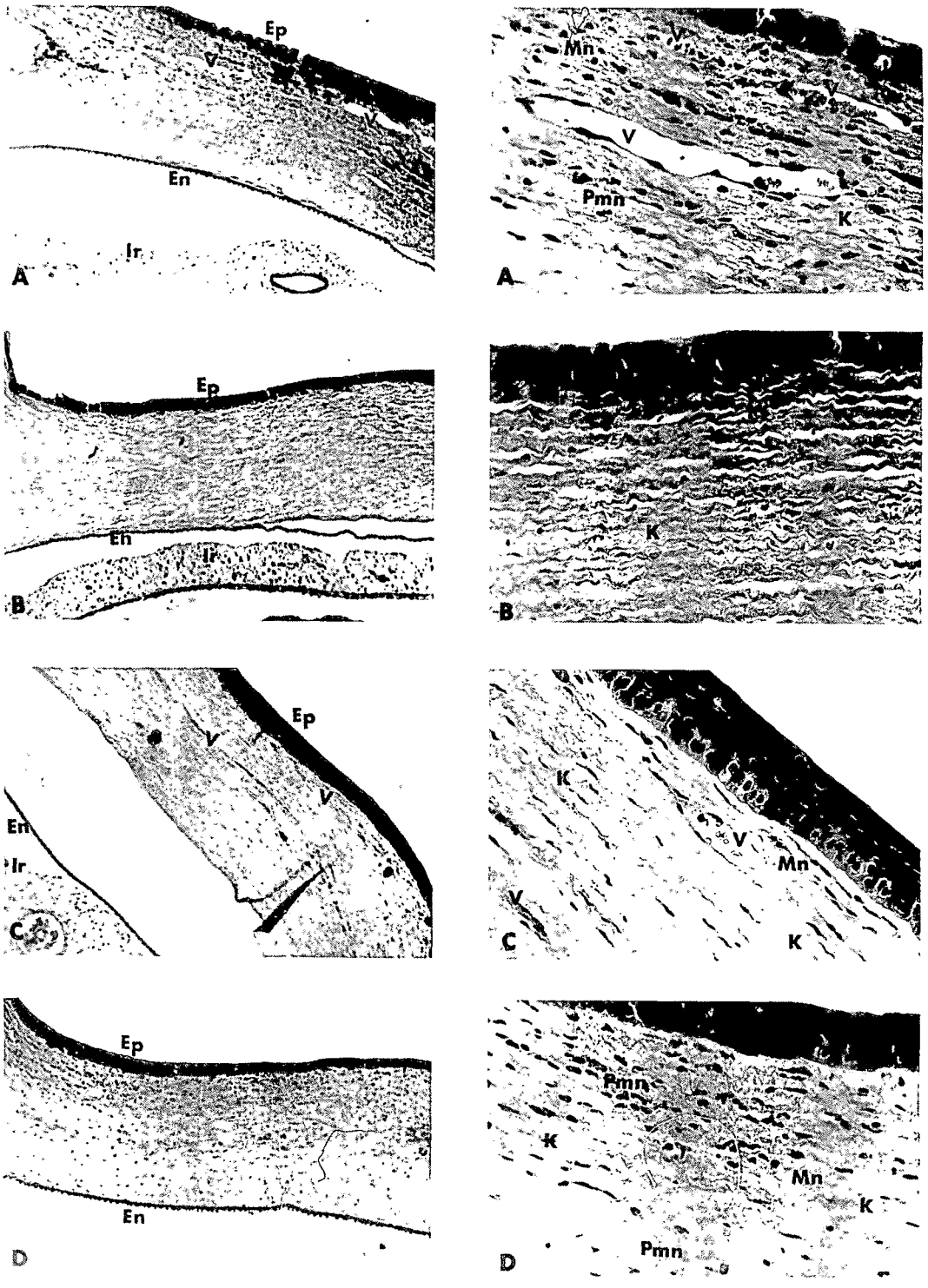


Fig. 1 (Ben Ezra). Cornea six days after insertion of the various implants. A, Implant sequestering 1 μg of PGE_1. The infiltrating new blood vessels reach the implant. Polymorphonuclear and mononuclear cells can also be observed. B, Empty implant of Elvax 40 (control). There is a slight corneal edema but no vessel or leukocyte invasion. C, A positive implant sequesters 10 μg of epidermal growth factor. Small vessels and a few monocytes are visible. Note the columnar configuration of basal cells and the relative hyperplasia of the epithelium. D, An implant sequestering 20 μg of formyl-methyonyl-leucine-phenylalanine shows an infiltration of leukocytes (mainly polymorphonuclear), but no neovascularization of the cornea. In B and C the Descemet's membrane is artifactually detached. Ep designates epithelium; V new vessel; Mn, mononuclear cells; Pmn, polymorphonuclear cells; K, keratocytes; En, endothelium; and Ir, iris (hematoxy-

TABLE 2

IN VIVO AND IN VITRO EFFECTS OF FIBROBLAST EPIDERMAL AND NERVE GROWTH FACTORS

Growth Factor	In vitro		Corneal Implants†	Cellular Proliferation‡	Neovascularization		
	Culture	CPM* ± S.D.			Length	Base	Surface
Fibroblast	Control	4,302±214	1.0 μg (12/0)	±	0.0	0.0	0.0
	+2 ng	10,243±679	10.0 μg (8/6)	+	0.5 ± 0.5	1.6 ± 1.2	1.3 ± 1.5
Epidermal	Control	3,934±272	1.0 μg (10/0)	+	0.0	0.0	0.0
	+2 ng	8,829±483	10.0 μg (7/6)	++	0.9 ± 0.6	2.1 ± 1.2	2.5 ± 2.2
Nerve	Control	4,378±264	1.0 unit(10/0)	0	0.0	0.0	0.0
	+1.0 unit	5,121±479	10.0 unit(6/0)	0	0.0	0.0	0.0

*CPM designates counts per minute.
†Numbers in parentheses indicate total number of implants per number demonstrating neovascularization.
‡Histologic observation corresponding to a mild keratocyte or epithelium proliferation, +; moderate to marked keratocyte or epithelial proliferation accompanied by vessel proliferation, ++; in vivo proliferation seldomly observed in histology sections, ±.

PGE_1 is the most active compound. PGE_2 stimulates a weaker vessel proliferation. Prostaglandins of the F series are much less active than the PGE, whereas PGA_1 and PGD_2 did not demonstrate any vasculogenic activity.

Prostaglandins are generated during the platelet aggregation reaction.[16] Platelets from patients with diabetes synthesize (and release) more prostaglandins than platelets from nondiabetics in the platelet aggregation reaction.[17] Also, PGE_2 in hypoxia might influence the sickling of erythrocytes.[18] Growing tumor cells as well as activated leukocytes and macrophages synthesize and release prostaglandins.[19–21] From these findings and the data presented in this paper regarding the strong neovasculogenic ability of PGE, ocular neovascularization may well be activated through these messengers. The vascular proliferation as observed in retrolental fibroplasia, diabetic retinopathy, sickle cell retinopathy, central retinal vein occusion, and chronic inflammatory or immune reactions can be rationalized

TABLE 3

COMPARISON BETWEEN IN VITRO CHEMOTAXIS AND IN VIVO ACTIVITY OF FORMYLATED SYNTHETIC PEPTIDES

Peptide*	Chemotaxis ED_{50}†	In vitro activity—20 μg per implant		
		No. of Implants	Cellular Infiltration	Neovascular
Meth-Phe	NA‡	19	(−)§	0
F-Meth-Phe	10^{-5}M	15	(−)	0
Meth-Leu	NA	16	(−)	0
F-Meth-Leu-Phe	10^{-9}M	23	(±)‖	0
Elvax-40	ND¶	32	(−)	0

*Meth-Phe designates methyonyl phenylalanine; F-Meth-Phe, formylmethyonyl-phynylalanine; Meth-Leu, methyonyl-leucine; and F-Meth-Leu-Phe, formyl-methyonyl-leucine-phenylalanine.
†ED_{50} designates effective dose inducing 50% of maximal chemotactic activity.
‡NA designates not active.
§ (−) designates no cellular infiltration.
‖ (±) designates few basophils and polymorphonuclear cells were observed near some of the implants sequestering formyl-methyonyl-leucine-phenylalanine.
¶ ND designates not done.

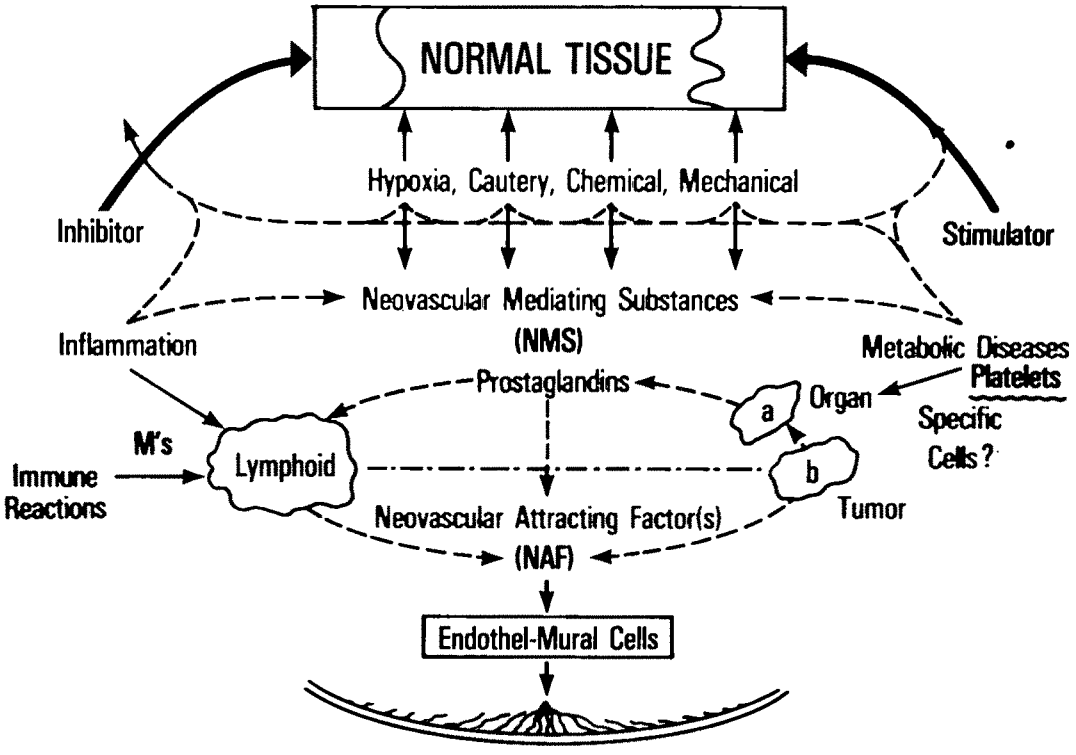


Fig. 2 (Ben Ezra). Diagrammatic representation of the possible reactions taking place during the various processes that may lead to the triggering of neovascularization.

on the basis of a local effect of prostaglandins. The undetermined Michaelson's x-factor of neovascularization, the tumor angiogenesis factor, and the neovascular attracting factor may be expressed by (or through) the release of identical compounds. Prostaglandins that fulfill the role of intercellular messengers and regulators of the immune response[19–21] may also play a central role in the regulation of neovasculogenesis (Fig. 2).

Fibroblast growth factor and epidermal growth factor activate the keratocyte DNA synthesis in vitro and variably induce the proliferation of keratocytes and epithelial cells in vivo at a concentration of 1 μg per implant. None of these, however, showed any neovasculogenic activity. In most cases, implants sequestering 10 μg of growth factor showed a small, but significant neovasculogenesis (Table 2). All implants sequestering formylated synthetic peptides were nonvasculogenic.

In this experimental design, whereas PGE_1 and, to some extent, PGE_2 fulfill the role of neovascular mediating substances, the role of other prostaglandins in regulating this activity is being studied. From the results of ongoing experiments, indomethacin does not seem to abolish the primary effect of prostaglandin E_1 on the triggering of blood vessel proliferation, but it does limit the perpetuation of the process and its extent (unpublished data).

The involvement of factors other than the stable prostaglandins in ocular neovascularization cannot be totally excluded. However, the important role of PGE in the initiation and perpetuation of this phenomenon appears most probable. The processes leading to corneal neovascular-

ization may differ from those leading to retinal or uveal neovascularization. However, as far as we know, the proliferation of new blood vessels in all ocular tissues is governed by the same basic mechanism. If this assumption is accurate, the use of inhibitors of prostaglandin synthesis may be an adequate approach for the prevention or the limitation of all neovascular phenomena.

SUMMARY

Prostaglandins E_1, E_2, D_2, A_1, $F_1\alpha$, and $F_2\alpha$ as well as synthetic chemoattractants and growth factors were tested for their ability to induce the proliferation of new blood vessels in the rabbit cornea. PGE_1 showed the strongest neovasculogenic activity attracting new blood vessels in all of the cases. PGE_2 was a weaker attractant than PGE_1. $PGF_2\alpha$ induced a less consistent reaction. All implants sequestering PGD_2 or PGA_1 were negative.

Implants sequestering 1 μg of fibroblast growth factor or epidermal growth factor variably stimulated the proliferation of keratocytes and epithelial cells in vivo. However, none of these demonstrated any vasculogenic activity. A small, but significant neovascularization was observed only in implants sequestering 10 μg of growth factor per implant. Although active in vitro, nerve growth factor and formylated synthetic peptides were not stimulatory in vivo.

ACKNOWLEDGEMENTS

J. L. Humes, Ph.D., and J. E. Pike, Ph.D., provided prostaglandins, and E. Schiffman, Ph.D., provided formylated peptides.

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SUBRETINAL NEOVASCULARIZATION FOLLOWING RUBELLA RETINOPATHY

KAY E. FRANK, M.D., AND EDWARD W. PURNELL, M.D.
Cleveland, Ohio

Rubella retinopathy is a commonly recognized complication of congenital rubella. Retinal pigmentation in a child with intrauterine rubella infection was first noted by Mitchell.[1] Subsequent reports confirmed this frequent sequela as an indication of intrauterine infection.[2–8] The usual appearance is retinal pigment clumping of the entire retina, although it is most marked in the macula.[3,6,9,10] In some cases, only the macula[1,9] or only one eye[6,9] may be involved. Rarely, a sector distribution occurs.[11,12] Although progressive changes in the fundus have been noted in children up to 17 months of age,[13,14] rubella retinopathy is considered a benign disorder which presents no threat to vision.[3,8–11] Subretinal neovascularization is not known to be a complication of this disorder.

We report herein two cases of subretinal neovascularization with a significant decrease in central vision in two older patients with rubella retinopathy.

CASE REPORTS

Case 1—A 17-year-old girl was seen because of metamorphopsia and decreasing vision in the right eye over a period of two weeks. Her mother had had a febrile illness with rash during the first trimester of pregnancy and serologic testing had confirmed the clinical diagnosis of rubella. At birth, no abnormality had been noted. Two years before the child's visit, visual acuity had been 6/6 (20/20) in both eyes. Initial visual acuity was R.E.: 6/12 (20/40); L.E.: 6/6 (20/20). Amsler grid examination indicated central metamorphopsia in the right eye and no abnormality in the left. The slit-lamp examination was unremarkable. Intraocular pressures were normal.

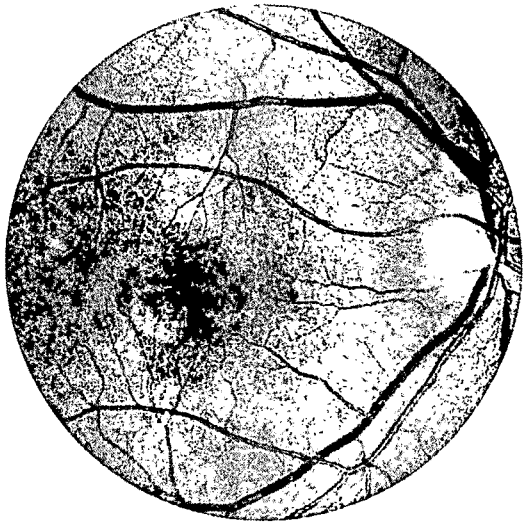


Fig. 1 (Frank and Purnell). Case 1. Fundus of right eye with macular pigmentary clumping, subretinal neovascularization, and hemorrhage.

Ophthalmoscopy revealed pigmentary clumping in the macula and the inferior nasal quadrant of the right eye (Fig. 1). In the macula a subretinal neovascular membrane was surrounded by hemorrhage.

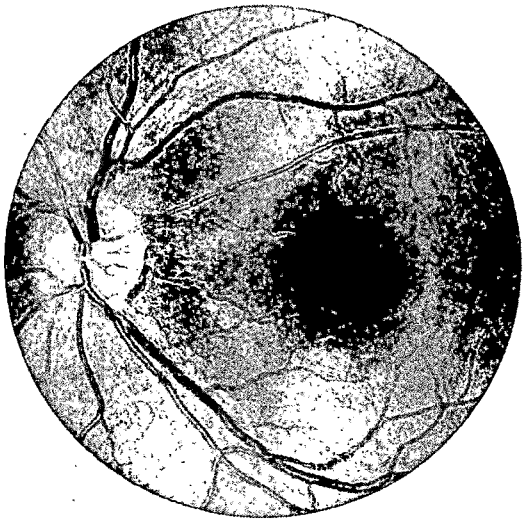


Fig. 2 (Frank and Purnell). Case 1. Normal fundus of left eye.

From the L. V. Johnson Laboratory, Division of Ophthalmology, Case Western Reserve University Hospitals, Cleveland, Ohio. This study was supported by the Ohio Lions Eye Research Foundation (Dr. Frank) and Research to Prevent Blindness, Inc. (Dr. Purnell).

Reprint requests to Kay E. Frank, M.D., Division of Ophthalmology, University Hospitals, 2065 Adelbert Rd., Cleveland, OH 44106.

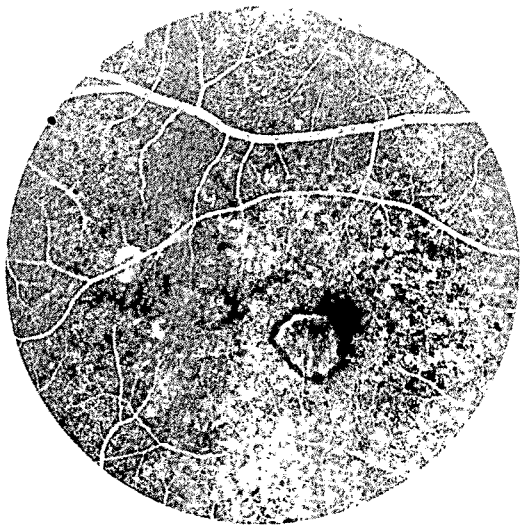


Fig. 3 (Frank and Purnell). Case 1. Early fluorescein angiogram of right eye showing transmission and blockage of choroidal fluorescence from pigmentary clumping as well as subretinal neovascularization.

The left eye was normal (Fig. 2). Fluorescein angiography confirmed the presence of a subretinal neovascular net (Fig. 3). Fifty milligrams per day of prednisone was given initially, and the dosage was gradually tapered during the next three months. At three months, there was fresh hemorrhage around the neovascularization (Fig. 4) and the visual acuity had decreased to 6/60 (20/200). Nine months after her initial visit, a disciform scar had formed. Her ophthalmoscopic appearance and visual acuity have not changed during the following two years (Fig. 5).

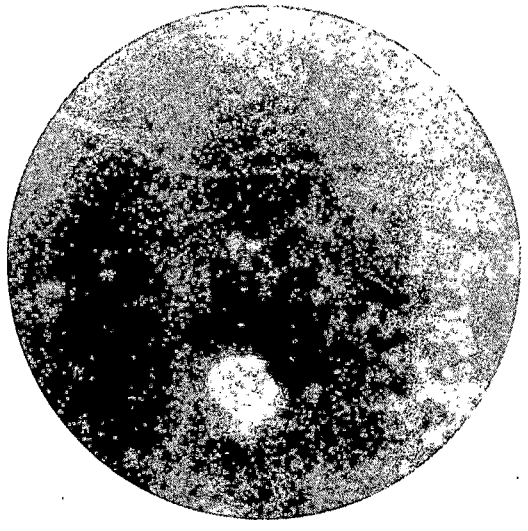


Fig. 4 (Frank and Purnell). Case 1. Late fluorescein angiogram of right eye showing leakage from subretinal neovascularization.



Fig. 5 (Frank and Purnell). Case 1. Fundus of right eye two years after onset of symptoms showing disciform scar.

Case 2—An 11½-year-old girl was seen because of blurred vision in the left eye for three weeks. During the first trimester of pregnancy her mother had had a febrile illness with rash, which had been diagnosed as rubella. During the child's first year, retinitis and deafness secondary to rubella had been diagnosed. Two years before this visit the visual acuity had been R.E.: 6/6 (20/20); L.E.: 6/7.5 (20/25), as measured by the referring ophthalmologist.

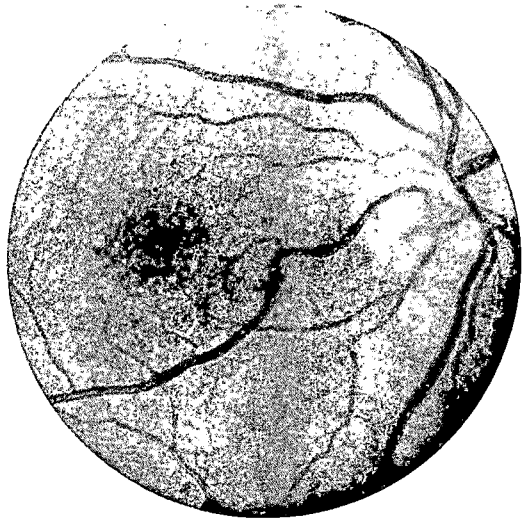


Fig. 6 (Frank and Purnell). Case 2. Fundus of right eye showing diffuse pigmentary clumping.

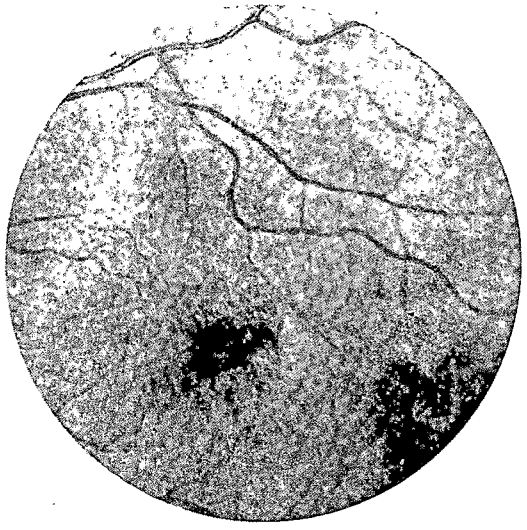


Fig. 7 (Frank and Purnell). Case 2. Fundus of left eye with diffuse pigmentary clumping and subretinal neovascularization and hemorrhage inferior to the fovea.

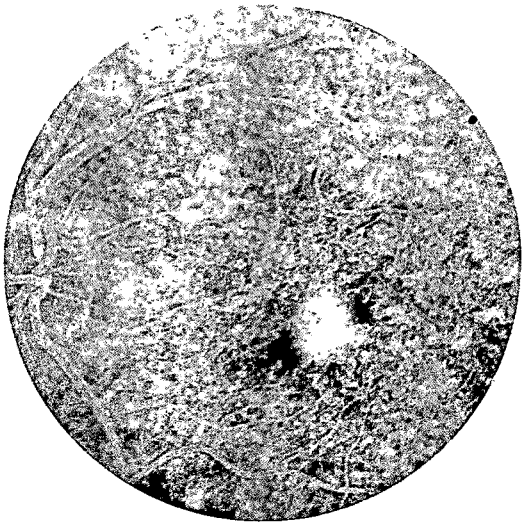


Fig. 9 (Frank and Purnell). Case 2. Late fluorescein angiogram showing leakage from subretinal neovascularization.

On this visit, visual acuity was R.E.: 6/6 (20/20); L.E.: 6/21 (20/70). Amsler grid examination indicated no abnormality in the right eye and central metamorphopsia in the left. Slit-lamp examination and intraocular pressures were normal. Ophthalmoscopy revealed diffuse pigmentary clumping of the entire retina in both eyes (Fig. 6). In the left eye inferior to the fovea there was a subretinal neovascular membrane with surrounding hemorrhage (Fig. 7). Fluorescein angiography confirmed the presence of the subretinal neovascular membrane (Figs. 8 and 9). No therapy was given. Follow-up examination one year later showed clearing of the hemorrhage



Fig. 8 (Frank and Purnell). Case 2. Early fluorescein angiogram of left eye showing transmission and blockage of choroidal fluorescence from pigmentary clumping as well as subretinal neovascularization.

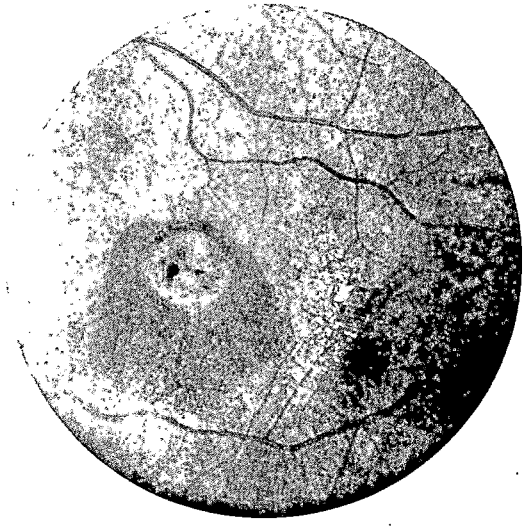


Fig. 10 (Frank and Purnell). Case 2. Macula of left eye showing growth of subretinal neovascularization and fresh hemorrhage 1½ years after appearance of neovascularization.

with no change in the size of the neovascularization. Visual acuity was 6/27 (20/90). Follow-up examination 1½ years later showed further growth of the neovascular membrane with fresh surrounding hemorrhage (Fig. 10). Visual acuity had decreased to 6/60 (20/200).

Discussion

Rubella retinitis is one of the most common ocular abnormalities noted after congenital rubella. There is widespread retinal pigment mottling or clumping with normal retinal vessels. The retinitis itself has no effect on visual acuity, although associated cataracts or optic atrophy from glaucoma can cause severe visual dysfunction.

Similar pigmentary changes have been noted in Leber's amaurosis or syphilis. In Leber's amaurosis, however, visual function is markedly diminished. Syphilitic retinitis can be differentiated by serologic testing.

Both patients had typical findings of rubella retinitis. Both demonstrated pigmentary clumping, normal retinal vessels, and good visual acuity until the onset of subretinal neovascularization. In both instances, there was a history of rubella infection during the mother's pregnancy. In Case 1, serologic testing for rubella had been performed, and in Case 2, deafness, another common complication of rubella, was present. Subretinal neovascularization has only been reported in four patients with rubella retinopathy.[15,16]

Subretinal neovascularization most frequently occurs as a consequence of senile choroidal macular degeneration,[15] but is uncommon in youth. Presumed ocular histoplasmosis syndrome is another common cause of subretinal neovascularization and can occur in young people.[15] Neither patient, however, showed findings consistent with presumed ocular histoplasmosis, and skin and complement fixation tests in Case 1 were negative for histoplasmosis. Other reported causes of subretinal neovascularization are angioid streaks, optic nerve drusen, myopia, choroidal rupture, traumatic scars, and choroidal tumors,[17] all of which can be excluded on the basis of the ophthalmoscopic and angiographic findings. Idiopathic subretinal neovascularization has been reported without retinal changes, but again this is an unlikely cause in such young patients.[18]

Subretinal neovascularization from other causes is commonly thought to result from disruption or degeneration of Bruch's membrane.[15] Pathologic findings in rubella retinitis, however, showed changes limited to the pigment epithelium.[19] The presence of subretinal neovascularization in rubella retinitis suggests that either the pigment epithelium plays a greater part in preventing subretinal neovascularization than previously appreciated or that damage to Bruch's membrane may occur in rubella retinitis and has not been detected histologically.

Summary

A 17-year-old girl and an 11-year-old girl with rubella retinopathy had decreased vision in one eye secondary to subretinal neovascularization and hemorrhage. In both cases a disciform scar with permanent decrease in central vision resulted.

Acknowledgments

C. K. Koster, M.D., and J. Sweeney, M.D., referred the patients for study.

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A FOLLOW-UP STUDY BY VITREOUS FLUOROPHOTOMETRY OF EARLY RETINAL INVOLVEMENT IN DIABETES

JOSE G. CUNHA-VAZ, M.D., JOSE R. FONSECA, M.D.,
JOSE F. ABREU, M.D., AND MANUEL A. RUAS, M.D.
Coimbra, Portugal

In a recent report on vitreous fluorophotometry, which is a new clinical method for the study of the blood-retinal barrier, a number of diabetic patients who had different degrees of retinal involvement showed a significant breakdown of the blood-retinal barrier when examined by vitreous fluorophotometry.[1] Furthermore, the disturbance of the blood-retinal barrier appeared before any clinically visible lesion of the fundus, a finding that has since been confirmed.[2] Vitreous fluorophotometry, therefore, has opened new possibilities for quantitative sensitive studies on the evolution of diabetic retinopathy and, particularly, its earlier stages.

We describe herein a series of diabetic patients who had no clinically visible retinal lesions and who were examined by vitreous fluorophotometry for a maximum period of 30 months. The values of breakdown of the blood-retinal barrier registered during this period were correlated with the degree of control of the diabetic disease, duration of diabetes, and development of vascular lesions in the retina.

SUBJECTS AND METHODS

The permeability of the blood-retinal barrier was assessed by vitreous fluorophotometry, the apparatus and techniques of which have been previously described.[1] In our study, a different fiberoptic probe with a 75 × 2,500-μ slit-shaped aperture was used. The macular region was selected for starting the recordings. The recordings from the retina to the lens were divided into three equal parts, which were ascribed to posterior vitreous, middle vitreous, and anterior vitreous. Only posterior vitreous values were taken into consideration for our study.

Every patient was tested for visual acuity and examined by direct ophthalmoscopy and fluorescein angiography before vitreous fluorophotometry. Fluorescein angiography was performed using either a camera with Baird Atomic filters or a Topcon TRC-F_3 with original filters. A series of photographs taken at one-second intervals was followed by additional photographs taken at five, ten, 15, and 30 minutes by using Tri-X-Pan film.

An injection of 1 g of sodium fluorescein, administered either as a 10% or 20% solution, was immediately followed by fluorescein angiography. Vitreous fluorophotometry was performed exactly one hour after the injection.

The diabetic patients included in our study (Table 1) were selected on the basis of the following criteria: (1) apparent retinal normality in the initial examination. "Normality" was determined after visual acuity testing and normal ophthalmoscopy and fluorescein angiography examinations. (2) Three examinations by vitreous fluorophotometry performed at approximately one-year intervals (F_0, F_1, F_2). In general, the patients included were examined in July or August 1975 (F_0), November or December 1976 (F_1), and Novem-

From the Departments of Ophthalmology (Drs. Cunha-Vaz, Fonseca, and Abreu) and Endocrinology (Dr. Ruas), University Hospital, Coimbra, Portugal. This study was supported by grants from Instituto National de Investigação Cientifica, Portugal and by Research to Prevent Blindness, Inc. (Dr. Cunha-Vaz).

Reprint requests to Jose G. Cunha-Vaz, M.D., Department of Ophthalmology, University of Illinois Eye and Ear Infirmary, 1855 W. Taylor St., Chicago, IL 60612.

TABLE 1

SUMMARY OF PATIENT DATA

Patient No.	Age, Sex (yrs)	Duration of Diabetes (yrs)	Therapeutics
1	46,M	8	Diet and oral
2	42,F	4	Diet and oral
3	60,M	5	Diet and oral
4	62,F	3	Diet and oral
5	80,F	8	Diet and oral
6	60,F	8	Diet and oral
7	59,M	3	Diet and oral
8	65,M	6	Diet and oral
9	50,F	6	Diet and oral
10	39,M	3	Diet and oral
11	65,F	5	Diet and oral
12	60,F	6	Diet and oral
13	67,F	3	Diet and oral
14	33,F	1	Diet and oral
15	62,F	7	Diet and oral
16	72,F	2	Diet and oral
17	49,M	2	Diet and oral
18	33,F	5	Insulin
19	44,M	3	Insulin
20	50,M	15	Insulin
21	28,F	4	Insulin
22	42,M	3	Insulin
23	41,M	3	Insulin
24	15,F	1	Insulin
25	74,M	6	Insulin

ber or December 1977 (F_2). Visual acuity, direct ophthalmoscopy, and fluorescein angiography were similarly performed at the time of the vitreous fluorophotometry. (3) Complete information about degree of diabetic metabolic control since the initial examination. These patients, all with confirmed diabetes, were observed in the Diabetic Clinic of the University Hospital of Coimbra.

The diabetes was considered to be under good control if one year before examination the patients had satisfied the following conditions: absence of major hypoglycemia symptoms; absence of ketoacidosis; satisfactory plasma glucose concentrations (50% of fasting determinations between 100 and 200 mg/dl and consistent total test values less than 250 mg/dl); 50% of all tests for glycosuria less than +; and absence of ketonuria. The patients were asked to test their own urine daily by using Ketostix and Clinistix. Furthermore, all the referred blood and urine tests were performed at a local laboratory at one-month intervals and at the university hospital at each clinic attendance, which was made at three-month intervals. The age of the patients and duration of the diabetic disease in the beginning of the study are shown (Table 1). The differences between the mean concentrations of fluorescein in the posterior vitreous from the different vitreous fluorophotometry examinations performed in each patient are accepted as showing the evolution in breakdown of the blood-retinal barrier, allowing for more or less penetration of fluorescein into the vitreous. Reproducibility studies and results from vitreous fluorophotometry examinations in normal volunteers have been previously reported.[1]

Further observations in normal volunteers older than 50 years of age have shown that vitreous fluorophotometry values increase with age. However, no values higher than 1.5×10^{-8} g/ml have been recorded in a total of 45 normal human eyes.

RESULTS

Vitreous fluorophotometry—All 25 patients included in this study had normal fundi at the initial examination. Despite the normality of the fluorescein angiograms, the vitreous fluorophotometry readings were constantly abnormally high, showing values of no less than 2.5×10^{-8} g/ml in the posterior vitreous (Table 2). The fluorescein concentration curves in the vitreous generally followed a typical pattern that showed higher values in the posterior vitreous, which clearly indicated a breakdown of the blood-retinal barrier. This alteration increased during the two-year follow-up period and showed a

TABLE 2

VITREOUS FLUOROPHOTOMETRY VALUES DURING FOLLOW-UP PERIOD

Patient No.	Diabetic Control	Angiographic Alterations	Vitreous Fluorophotometry $\times 10^{-8}$g/ml
		1975	
1	Good	-	6.5
2	Good	-	3.8
3	Good	-	7.4
4	Good	-	5.0
5	Poor	-	7.6
6	Good	-	2.7
7	Good	-	4.8
8	Good	-	7.0
9	Poor	-	5.2
10	Good	-	3.3
11	Good	-	8.3
12	Good	-	4.4
13	Poor	-	6.6
14	Good	-	5.4
15	Good	-	4.2
16	Poor	-	8.4
17	Poor	-	3.6
18	Poor	-	4.4
19	Poor	-	3.5
20	Poor	-	7.4
21	Good	-	2.8
22	Poor	-	6.0
23	Good	-	4.6
24	Poor	-	2.8
25	Poor	-	8.5
		1976	
1	Good	-	5.1
2	Good	-	5.3
3	Good	-	6.8
4	Good	-	5.8
5	Poor	2 Microaneurysms	9.1
6	Good	-	8.6
7	Good	-	6.5
8	Good	-	10.8
9	Poor	-	7.0
10	Good	-	3.6
11	Good	-	8.3
12	Good	-	4.0
13	Poor	-	9.0
14	Good	-	6.8
15	Good	-	5.0
16	Poor	2 Microaneurysms, hard exudates, leakage	9.9
17	Poor	5 Microaneurysms	9.4
18	Poor	-	6.4
19	Poor	-	5.3
20	Poor	-	11.4
21	Good	-	3.5
22	Good	-	5.4
23	Good	-	5.5
24	Poor	-	6.3
25	Poor	4 Microaneurysms	10.4

TABLE 2 (*Continued*)

VITREOUS FLUOROPHOTOMETRY VALUES DURING FOLLOW-UP PERIOD

Patient No.	Diabetic Control	Angiographic Alterations	Vitreous Fluorophotometry $\times 10^{-8}$g/ml
		1977	
1	Good	2 Microaneurysms	8.0
2	Good	-	3.6
3	Good	1 Microaneurysm	8.6
4	Good	1 Microaneurysm 2 Hard exudates	10.2
5	Poor	4 Microaneurysms, leakage	12.5
6	Good	-	9.5
7	Good	-	6.8
8	Good	-	7.5
9	Poor	1 Microaneurysm, hard exudates	9.8
10	Good	-	4.5
11	Good	-	8.4
12	Good	-	5.2
13	Poor	2 Microaneurysms	12.6
14	Good	-	7.6
15	Good	-	6.8
16	Poor	4 Microaneurysms, hard exudates	13.5
17	Poor	7 Microaneurysms, hard exudates, leakage	15.0
18	Poor	-	6.5
19	Poor	-	6.1
20	Poor	1 Microaneurysm	15.0
21	Good	-	3.0
22	Good	-	6.0
23	Good	-	6.9
24	Poor	-	8.0
25	Poor	Leakage, microaneurysms, capillary closure, hard exudates, maculopathy	34.0

clear progression with the evolution of the diabetic diease (Figure). This increase was particularly marked in patients whose diabetes was under poor metabolic control.

To examine more closely this apparent correlation between metabolic control and the alteration of the blood-retinal barrier in the earlier stages of retinal involvement in diabetes, we compared the differences between the vitreous fluorophotometry readings performed at approximately one-year intervals and between the final and initial examinations (F_2 to F_0) in two groups of patients considered to be either under good or poor metabolic control, according to the specifications of the studies. Statistical analysis of the vitreous fluorophotometry differences was performed in only 24 patients. Patient 25 was excluded from all statistical analyses because of his exceptionally marked retinal lesions and high fluorophotometric readings. Of the 24 patients, 15 remained under good control and nine under poor metabolic control

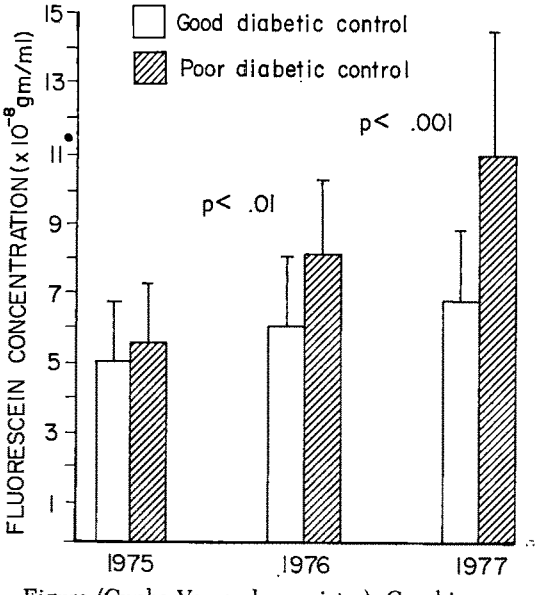


Figure (Cunha-Vaz and associates). Graphic representation of the mean values of abnormal fluorescein concentration in the posterior vitreous of a series of diabetic patients examined by vitreous fluorophotometry in 1975, 1976, and 1977.

TABLE 3

DIFFERENCES IN FLUORESCEIN PENETRATION INTO THE POSTERIOR VITREOUS BETWEEN THE LAST AND THE INITIAL EXAMINATION (F_2-F_0)*

Good Control		Poor Control	
Series No.	F_2-F_0	Series No.	F_2-F_0
1	+1.5	5	+ 4.9
2	−0.2	9	+ 4.6
3	+1.2	13	+ 6.0
4	+5.2	16	+ 5.1
6	+6.8	17	+11.4
7	+2.0	18	+ 2.1
8	+0.5	19	+ 2.6
10	+1.2	20	+ 7.6
11	+0.1	24	+ 5.2
12	+0.8	Mean	+ 5.5
14	+2.2	S.D.	± 2.8
15	+2.6		
21	+0.2		
22	±0		
23	+2.3		
Mean	±1.8		
S.D.	±1.9		

*t = 3.7; Df = 22; P<.001.

during the entire follow-up period. The statistical analysis of the comparison between the last and initial examinations revealed a significant difference (t=3.6; Df=22; P<.001; Table 3).

If all the results are taken into account and each interval between vitreous fluorophotometry examinations is considered (F_2 to F_1 and F_1 to F_0), 30 periods of approximately one year under good control can be compared with 18 similar periods under poor control. Statistical analysis revealed a significant difference between the vitreous fluorophotometry readings in patients under poor and good diabetic metabolic control (t=3.5; Df=48; P<.001; Table 4).

These results indicated that in patients under good metabolic control, the alteration of the blood-retinal barrier progresses much more slowly than in patients under poor control, at least for a follow-up period of approximately two years.

A correlation was also present between the vitreous fluorophotometry readings at the initial examination and previous duration of the diabetic disease. Patients who had diabetes for less than five years at the start of the study (Patients 2, 4, 7, 10, 13, 14, 19, and 21-24) showed a mean vitreous fluorophotometry reading of 4.7 ± 1.6 × 10^{-8} g/ml, whereas the other 11 patients who had diabetes for five years or more showed a mean reading of 5.9 ± 1.8 × 10^{-8} g/ml. The difference between these two means (t=1.73; Df=22; P<.05) is significant.

Fundus fluorescein angiography—Retinal lesions, including rare microaneurysms, capillary dilatations or signs of "leakage" on fluorescein angiography, hemorrhages, or hard exudates, appeared in four of the 25 eyes (16%) after the first year of follow-up and in ten (40%) at the end of the second year.

The retinal lesions observed were minimal; there were between one and ten microaneurysms. Only one patient

TABLE 4

DIFFERENCES IN FLUORESCEIN PENETRATION INTO THE POSTERIOR VITREOUS BETWEEN EACH VITREOUS FLUOROPHOTOMETRY EXAMINATION (F_2-F_1 and F_1-F_0)

Good Control			Poor Control		
Series No.	F_1-F_0	F_2-F_1	Series No.	F_1-F_0	F_2-F_1
1	−1.4	+2.9	5	+1.5	+3.4
2	−0.5	+0.3	9	+1.8	+2.8
3	−0.6	+1.8	13	+2.4	+3.6
4	+0.8	+4.4	16	+1.5	+3.6
6	+5.9	+0.9	17	+5.8	+5.6
7	+1.7	+0.3	18	+2.0	+0.1
8	+3.8	−3.3	19	+1.8	+0.8
10	+0.3	+0.9	20	+4.0	+3.6
11	±0	+0.1	24	+3.5	+1.7
12	−0.4	+1.2	Mean	+2.8	
14	+1.4	+0.8	± S.D.	±1.5	
15	+0.8	+1.8			
21	+0.7	−0.5			
22	−0.6	+0.6			
23	+0.9	+1.4			
Mean	+0.9				
± S.D.	±1.7				

*t = 3.9; Df = 46; P<.001.

showed rapid progression to a condition of maculopathy and marked vessel leakage.

The chances of developing retinal lesions, therefore, appear to increase as vitreous fluorophotometry readings increase (Figure). Some correlation is also apparent between duration of the disease and development of retinal lesions. Of the 13 patients who at the start of the study had diabetes for less than five years, only four developed retinopathy (30%), whereas of the 11 patients who had diabetes for five years or more, five (45%) developed retinopathy.

Analysis of the vitreous fluorophotometry values in eyes that revealed retinal lesions on fundus fluorescein angiography showed that all had values of 8×10^{-8} g/ml or greater in the posterior vitreous, the average being 11.1×10^{-8} g/ml. This clearly contrasted with those values recorded in "normal" diabetic eyes that showed an average value of 5.9×10^{-8} g/ml, with values less than 8×10^{-8} g/ml in 50 (82%) of them. A vitreous fluorophotometry value of 11.4×10^{-8} g/ml was recorded in an eye showing a normal angiogram.

Finally, retinal lesions appeared to develop preferentially in patients under poor diabetic control. Of the ten eyes that developed a retinopathy, seven were from patients who were under poor metabolic control. This finding is even more relevant if a comparison is made to the incidence of retinopathy in patients under good metabolic control (three of 15 [20%]) for the same period of follow-up.

DISCUSSION

To evaluate the alteration of the blood-retinal barrier, its change during the period of follow-up, and its correlations with diabetic metabolic control, duration of the disease, and development of retinal lesions, we accepted the differences between the mean concentrations of fluorescein in the posterior vitreous obtained in the vitreous fluorophotometry examinations as indications of more or less pene-

tration of fluorescein into the eye, namely, the degree of breakdown of the blood-retinal barrier.

The results showed that the alteration of the blood-retinal barrier increased generally during the two-year follow-up period, and that this increase was particularly marked in the diabetic patients who were under poor metabolic control.

In the earlier stages of retinal involvement in diabetes, poor metabolic control and progression in the breakdown of the blood-retinal barrier correspond, as shown by vitreous fluorophotometry. In a study of rats made diabetic with streptozotocin, Waltman and associates,[3] by using vitreous fluorophotometry, have similarly shown that the breakdown of the blood-retinal barrier is the first change to occur in the retina and that the degree of breakdown improved immediately after institution of appropriate diabetic treatment and adequate metabolic control.

We demonstrated a significant association between degree of breakdown of the blood-retinal barrier and duration of the diabetic disease, independent of the type of diabetes involved.

In our study, retinal lesions developed in four of 25 (16%) of the eyes after the first 18 months of follow-up, and in ten of 25 (40%) at the end of the 30-month period.

Development of retinal lesions in diabetes, which follows the earlier breakdown of the blood-retinal barrier, appears to be associated with the progressive alteration of the barrier, as shown by vitreous fluorophotometry. The average value recorded in the posterior vitreous in diabetic eyes showing a normal fundus was 5.9×10^{-8} g/ml in contrast with an average value of 11.1×10^{-8} g/ml in eyes with minimal retinal lesions.

Similarly, the development of retinal lesions appears to be associated with longer duration of the diabetic disease and with poor metabolic control. However, in diabetes, the breakdown of the blood-retinal barrier may act as a link between the degree and duration of departure from metabolic abnormality and the development of retinal lesions.

The results of our study suggest that, in diabetic patients, an increase in vitreous fluorophotometry values, indicative of a progression in the breakdown of the blood-retinal barrier, is directly associated with development of retinal lesions, and that close control of diabetes reduces the frequency of retinopathy, possibly by acting favorably on the breakdown of the blood-retinal barrier.

Summary

A series of 25 diabetic patients who showed apparently normal fundi on ophthalmoscopy and fundus fluorescein angiography were observed by using vitreous fluorophotometry for 30 months. The results showed that the alteration of the blood-retinal barrier increased generally during the follow-up period, particularly in the diabetic patients who were under poor metabolic control. The degree of breakdown of the blood-retinal barrier was significantly associated with the duration of the diabetic disease.

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USE OF A XENON FLASH TUBE AS THE EXCITATION SOURCE IN A NEW SLIT-LAMP FLUOROPHOTOMETER

RICHARD F. BRUBAKER, M.D., AND ROGER L. COAKES, F.R.C.S.
Rochester, Minnesota

The use of fluorescein as a marker dye for studying ocular fluid dynamics is well established[1–8] and has been reviewed thoroughly by Maurice.[9] Instruments capable of making measurements of fluorescein concentration in living ocular tissues have been previously described.[10–13] Each of these instruments has been designed to meet specific needs in a research environment.

Previously described fluorophotometers have used sensitive photomultiplier tubes and bright, sometimes specially constructed sources of illumination to extend the range of measurement to low concentrations of fluorescein. To reduce the effect of background illumination, some instruments have been provided with a system of chopper stabilization. Nevertheless, these instruments must be used under darkroom conditions for alignment of the target area, achievement of measurement stability, or protection of the photomultiplier tube.

Some of the inconvenient aspects of fluorophotometry in human subjects can be circumvented by using a xenon flash tube as the source of light for excitation of fluorescence. We describe herein a new fluorophotometer that uses such a light source.

MATERIAL AND METHODS

The fluorophotometer is a modified Zeiss photo-slit lamp camera. The fluorescein measurement is made during a single flash, much the same as the use of the camera system in photographing the eye. The fluorophotometer consists of two parts, the modified slit-lamp camera and the control unit.

The slit-lamp camera is modified in four ways (Fig. 1). First, the left camera is replaced by a sensitive photomultiplier tube (PMT "F"), which is protected by a shutter. The photomultiplier tube housing contains the barrier filter (Baird-Atomic B-5 combined with Wratten 15), and a two-position field-limiting aperture that defines the windows for measuring fluorescein mass or fluorescein concentration. The mass aperture includes the entire field of view and contains a 3.0 neutral density filter. The concentration aperture is a crescent-shaped slit 15 mm long and 1 mm wide with a radius of curvature of 34.3 mm. At × 40 magnification, the projected size of this aperture in the object plane is 3.0 × 0.2 mm and has the same curvature as the midsagittal plane of

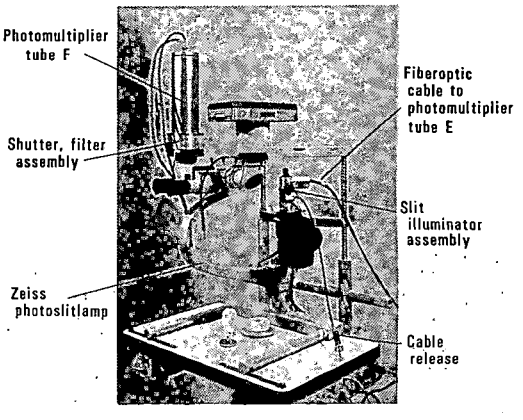


Fig. 1 (Brubaker and Coakes). Zeiss slit lamp camera system illustrating location of modifications needed for performing quantitative fluorophotometry.

From the Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota.

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Reprint requests to Richard F. Brubaker, M.D., Mayo Clinic, Rochester, MN 55901.

the normal human cornea as viewed from 55 degrees (the concentration aperture is removable so that apertures of other sizes or shapes can be substituted if needed for special purposes; Fig. 2). Second, the left eyepiece contains a reticle with a central dot which is aligned with the center of the field where fluorescence is to be measured (Fig. 3). Third, the right-angle prism assembly that deflects the slit beam has been modified by the addition of an excitation filter and a beam splitter. The excitation filter can be brought into the slit light pathway by depressing a cable release or foot switch. This modification permits the examiner to align the instrument on the target by using white light before triggering a measurement. The additional beam splitter provides a second photomultiplier tube (PMT "E") with a sample of the excitation beam (about 4%) (Fig. 2). The fourth slit-lamp modification is the addition of a silicon-controlled rectifier to the flash trigger circuit. This modification allows the flash tube to be triggered by an electronic signal from the control unit.

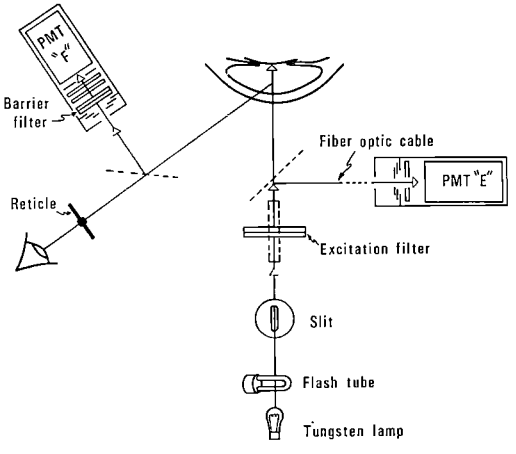


Fig. 2 (Brubaker and Coakes). Optical pathways of fluorophotometer. Fluorescence field-limiting aperture located adjacent to barrier filter. Eyepiece reticle optically aligned with center of field-limiting aperture. Excitation filter can be rotated into or out of slit light pathway.

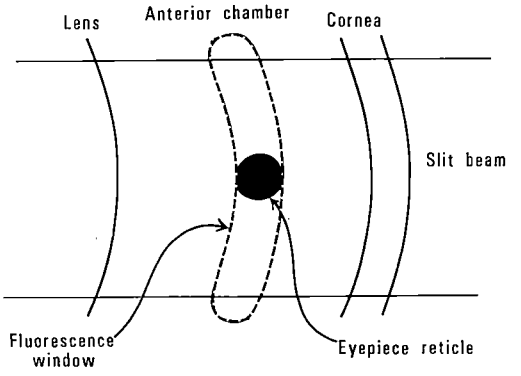


Fig. 3 (Brubaker and Coakes). Observer's view of eye during concentration measurement. Eyepiece reticle (visible to observer) optically aligned with fluorescence field limiting aperture (not visible to observer).

The control unit was designed to perform the following functions: open and close the photomultiplier shutters, trigger the flash tube, do data processing of the photomultiplier signal, and display the concentration or mass of fluorescein. A timer circuit controls the sequence and duration of events that take place during each measurement. The sequence is initiated by depressing a cable release or foot switch that snaps the blue excitation filter into the slit beam. The photomultiplier shutters open, and the output of each photomultiplier tube is integrated for 16.7 msec (duration of one cycle at 60 Hz) to determine the level of background illumination (Fig. 4). During the next 16.7-msec period, the flash is discharged and the output of each photomultiplier tube is integrated to determine the intensity of the excitation beam and the intensity of fluorescence (Fig. 5). The photomultiplier shutters open for 0.1 second, then close.

The output of each photomultiplier is processed concurrently with the measurement. The integral of the first period (the background) is subtracted from the integral of the second period (the gross signal) to produce the net signal from each tube. The net signal from the fluores-

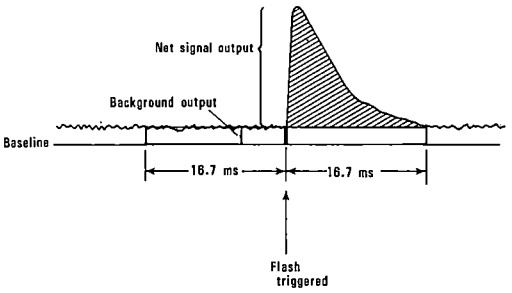


Fig. 4 (Brubaker and Coakes). Photomultiplier tube output as it appears from each tube, PMT "E" and PMT "F".

cence photomultiplier tube (PMT "F") is divided by the net signal from the excitation photomultiplier tube (PMT "E"). The dividend is proportional to fluorescein mass or concentration and is independent of flash intensity or slit width. The output of the divider can be scaled to be displayed and printed in absolute mass or concentration units. The individual components used in the system are listed (Table 1).

A commercially available solution of 10% sodium fluorescein (Funduscein) was used for instrument calibration. The accuracy of the stock solution was verified by using a Beckman DU-2 spectrophotometer set at 493 nm. Standards were prepared by making serial dilutions in neutral 0.1M phosphate buffer of this stock solution.

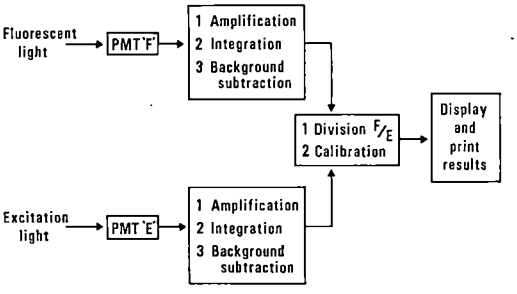


Fig. 5 (Brubaker and Coakes). Signal processing by control unit. Background signal subtracted from each photomultiplier output to eliminate the effect of background illumination. Signal from PMT "F" (fluorescent intensity) is divided by signal from PMT "E" (excitation intensity) to correct for variations in flash intensity and slit width.

A calibration cell was made that could be attached conveniently to the chin rest of the slit lamp. The cell consisted of a corneal contact lens and a vertical black plastic surface to which the water-filled lens would adhere by capillary attraction. The contact lens was 9.0 mm in diameter and 0.5 mm thick, had a front radius of curvature 7.8 mm and a back radius of curvature 7.3 mm, and contained 45 μl of the test solution.

The extinction coefficient, ϵ, for fluorescence measurement with this instrument was measured by using solutions of 10 μg/ml and a modified cell that could be moved along the slit beam axis with a calibrated screw adjustment. Measurements of fluorescence were made by using the nominal concentration settings shown in Table 2. Fluorescence was measured at two depths in the calibration cell, separated 1.0 mm, by changing the screw adjustment of the cell holder. The value of ϵ was determined from the relation

$$\epsilon = \frac{\ell n \left(\frac{F_1}{F_2}\right)}{C \cdot \Delta X} \qquad (1)$$

where F_1 and F_2 were the fluorescence readings at the two depths in the cell separated by the distance ΔX of 1.0 mm and C was the concentration of fluorescein in the calibration cell.

The stability of instrument readings was checked over several eight-hour periods. During some stability checks, the power was turned off between hourly readings and during others, the power was left on. Day-to-day stability was checked over a period of several weeks. Two standards were used for these tests, a fluorescent glass standard, equivalent to a

TABLE 1

MAJOR SYSTEM COMPONENTS

Component	No. Needed	Manufacturer's Identification
Zeiss photo slit-lamp system	1	Zeiss 31-03-29
Photomultiplier tubes	2	EMI 9635B
Excitation filter	1	Baird-Atomic (B-4) 33-18-50
	1	Eastman Kodak, Wratten 47B
Barrier filter	1	Baird-Atomic (B-5) 33-42-80
	1	Eastman Kodak, Wratten 15
Neutral density filters	2	Baird-Atomic (ND 1.0) 86-97-00
	2	Baird-Atomic (ND 2.0) 86-98-90
Fluorescent glass standard	1	Corning yellow filter No. 3750
Shutters	2	Vincent 225L2A6X5
Shutter control	2	Vincent 100-2
High voltage power supply	1	Power Designs AEC-315B
Control unit	1	(Custom-built)*

*Detailed plans available on request.

fluorescein solution of 3.92×10^{-6} g/ml, and a fluorescent plastic standard fabricated of sodium fluorescein in methyl methacrylate, equivalent to a fluorescein solution of 3.68×10^{-8} g/ml.

The effect of background illumination on instrument performance was measured with an International Light, Model IL-700, Radiometer/Photometer using the SEE-400 photopic filter (CIE response, 2580.85° C color temperature calibration source). The light-sensitive element was placed over the slit-lamp objective during background light measurements. Background light of 0.01, 0.1, 1.0, and 10 foot candles was produced from fluorescent lamp sources. Concentration and mass measurements of fluorescein standards, water blanks, and the normal anterior chamber and cornea of the human eye were measured at each of these levels of background illumination.

The effect on anterior chamber concentration measurements of high concentra-

TABLE 2

NOMINAL SLIT-LAMP SETTINGS FOR MEASUREMENTS OF CONCENTRATION AND MASS

	Concentration		Mass	
	Possible Range	Usual Setting	Possible Range	Usual Setting
Slit setting				
Width	0.05-0.2 mm	0.1	3.0-10 mm	10 mm
Height (diameter)	0.3-3.0 mm	3.0	3.0-10 mm	10 mm
Photomultiplier tube "F"				
Field aperture	Any size or shape up to entire field	3.0 × 0.2 crescent-shaped slit	Any size or shape up to entire field	Entire field
Neutral density filter	0-3.0	None	2.0-5.0	3.0
F stop	F11-F32	F22	F11-F32	F22
Photomultiplier tube "E"				
Neutral density filter	0.0-3.0	1.0	3.0-6.0	4
Observation angle	60 degrees-45 degrees	55 degrees	10 degrees-20 degrees	10 degrees
Magnification	6×-40×	40×	6×-16×	6×
Flash intensity	1-4	2	1-4	2

tions of fluorescein in the cornea was tested in the living monkey eye and in the living human eye. In the monkey eye, fluorescein was placed into the central cornea by using the iontophoretic technique of Jones and Maurice.[6] The anterior chamber was kept free of fluorescein by rapid two-needle perfusion with an aqueous humor substitute. Concentration readings were taken in the central cornea and the central anterior chamber every 15 minutes for three hours. In 15 normal human subjects (30 eyes), from 0.1 to 1.0 μg of fluorescein was placed into the central cornea by iontophoresis, using a 4-mm diameter agar electrode. Concentration readings were taken immediately afterward in the central cornea and the central anterior chamber. In the fluorescein-free anterior chamber, the fluorescence in the cornea produced an apparent concentration, which was a constant fraction about 1.2%, of the corneal fluorescence.

The position sensitivity in the excitation field for mass measurements was tested with a small fluorescent droplet. The mass of fluorescein in the droplet was measured in various portions of the excitation field (9.5 mm in diameter).

The accuracy of corneal mass measurements was determined in enucleated rabbit eyes. Nine freshly enucleated eyes were used. The central 4 mm of the corneal epithelium was marked with a trephine and scraped off with a sharp blade. The cornea was excised and placed over the corneal contact lens of the water-filled calibration cell described above. One microliter of fluorescein solution of known concentration was placed from a micropipet as a droplet over the denuded area and allowed to diffuse into the cornea for five minutes. (A total mass of 1.0 μg was placed on three corneas, 0.5 μg on three others, and 0.1 μg on three others). The calibration cell was mounted on the slit lamp and a measurement made of the total fluorescein mass in each cornea.

The effect of iris reflectance from light colored irides on corneal mass measurement was determined. The reflection of the excitation beam from eyes containing no fluorescein was measured in human subjects by sliding out the barrier filter of the fluorophotometer. Reflectance of five human subjects whose iris color varied from dark brown to light blue was measured and compared to reflectance through a contact lens of various textured surfaces from flat black to white. The effect on corneal fluorescein mass measurement of "iris" reflectance encompassing the range found in human subjects was measured by using these calibrated surfaces and excised rabbit corneas containing a central depot of fluorescein.

RESULTS

The results of instrument calibration with standard solutions of fluorescein are shown (Table 3). Concentration readings were within 3% of linear over the range 10^{-8} to 10^{-5} g/ml. The mean reading of 10^{-9} g/ml was within 15% of the expected value if a blank reading were subtracted, but the individual readings were much more scattered. Extinction of the excitation beam did not permit linear measurement of concentrations of 10^{-4} g/ml or greater (Table 3).

Mass readings in the 45 μl calibration cell were most reliable in the range of 4.5×10^{-8} to 4.5×10^{-7} g. The mean reading at 4.5×10^{-9} g was within 12% of the expected reading, but the individual readings were much more scattered. When a solution of 10^{-4} g/ml was used in the mass calibration cell, extinction of the excitation beam by the high concentration of fluorescein was sufficiently great to reduce the mass reading to nearly half the expected reading. The optimum range for measuring mass of fluorescein with this instrument appears to be between 1×10^{-8} and 1×10^{-6} g.

The anterior chamber of the human eye gave a concentration reading approxi-

TABLE 3

FLUOROPHOTOMETER CALIBRATION*

Concentration, g/ml				Mass, g			
Fluorescein Standard (g/ml)	Instrument Reading Mean	SE	×	Fluorescein Standard (g/0.045 ml)	Instrument Reading Mean	SE	×
Blank	−0.36	0.16	10^{-9}	Blank	0.39	0.58	10^{-9}
1×10^{-9}†	1.13	0.33	10^{-9}				
1×10^{-8}	1.01	0.09	10^{-8}				
1×10^{-7}	1.02	0.01	10^{-7}	4.5×10^{-9}†	5.03	0.61	10^{-9}
1×10^{-6}‡	1.00	0.003	10^{-6}	4.5×10^{-8}‡	4.50	0.08	10^{-8}
1×10^{-5}	1.03	0.005	10^{-5}	4.5×10^{-7}	4.38	0.05	10^{-7}
1×10^{-4}	0.55	0.006	10^{-4}	4.5×10^{-6}	2.35	0.01	10^{-6}
Fluorescent plastic standard	3.68	0.04	10^{-8}				
Fluorescent glass standard	3.92	0.001	10^{-6}		3.09	0.04	10^{-7}
Human eye							
Anterior chamber	1.49	0.11	10^{-9}				
Cornea	1.30	0.04	10^{-8}				
Anterior segment					5.97	0.28	10^{-9}

*Mean ± SE, five determinations; background illumination at slit-lamp objective equals 0.1 foot candle.
†Reading corrected for blank solution.
‡Concentration reading standardized using 1×10^{-6} g/ml; mass reading standardized using 45 μ of 1×10^{-6} g/ml = 4.5×10^{-8} g.

mately equivalent to 1.5×10^{-9} g/ml, whereas the reading in the normal cornea was approximately equivalent to a solution of 1.3×10^{-8} g/ml. The blank mass reading of the eye was found to be about ten times the water blank, about 6×10^{-9} g.

The level of background illumination falling on the camera objective did not affect instrument readings at higher ranges, but did affect instrument readings at lower ranges of concentration and mass. Table 4 outlines the limits of background illumination required for the instrument reading be in error less than 5%. We used the instrument in a room illuminated by a single 15-W fluorescent desk lamp directed at a writing surface behind the examiner's side of the slit lamp. This lamp illuminates the objective approximately 0.1 foot candle, yet provides enough light to seat the subject, operate the fluorophotometer, and record the results. The background illumination can be checked easily by sliding out the barrier filter, setting the output selector switch to "Background," and triggering a measurement.

No statistically significant drift occurred in measurement of the fluorescence of the plastic and the glass standards over an eight-hour period if the instrument was left on continuously or turned off between hourly measurements. The standard deviation in the measurements taken hourly was 2% of the daily mean. There was no statistically significant drift over several weeks' period of testing. Variations in the reading taken from day to day with both standards ap-

TABLE 4

LIMITS OF BACKGROUND ILLUMINATION*

Minimum Concentration or Mass to be Measured	Maximum Allowable Illumination on Slit-Lamp Objective, foot candle
1.0×10^{-8} g/ml	0.1
1.0×10^{-7} g/ml	1.0
1.0×10^{-6} g/ml	10.0
4.5×10^{-8} g	0.1
4.5×10^{-7} g	1.0
4.5×10^{-6} g	10.0

*For accurate fluorophotometric measurements; background error < 5% of minimum measurement.

peared to be entirely random. The standard deviation in the measurements taken daily over several weeks' time was 3% of the mean. These tests indicate that frequent standardization is unnecessary unless measurements of great accuracy are needed.

The ability of the control unit to compensate for variations in slit width and flash intensities is shown (Table 5). Although the excitation energy varied by a factor of more than 20, the output of the system varied 2% or less. The data indicate that small variations in flash output or slit width during operation of the fluorophotometer will have no significant effect on the results.

The extinction coefficient, ϵ, for this system of measurement was $2.22 \times 10^5 \pm 0.32$ cm^2 g (mean ± SE, n=4). The intensity of fluorescence along the path length of the slit beam can be predicted from the following relation:

$$F = F_o e^{-\epsilon \cdot C \cdot \Delta\chi} \quad (2)$$

where F_o is the fluorescent intensity at the surface, F is the fluorescent intensity at a depth $\Delta\chi$ into the eye, and C is the concentration of the fluorescein solution in the media of the eye. Our data indicate that at fluorescein concentrations under 10^{-6} g/ml, measurements in the anterior chamber can be made without correcting for extinction, but above concentrations of 10^{-6} g/ml, corrections for extinction are necessary (Table 6).

High levels of corneal fluorescence affected the measurement of low levels of anterior chamber fluorescein concentration, an effect that existed only when the excitation beam passed through the corneal depot. In the monkey eye, the apparent fluorescence measured in the center of the fluorescein-free anterior chamber was a constant fraction of the fluorescein concentration in the portion of the cornea through which the excitation beam passed when anterior chamber measurements were made. The same phenomenon was observed in human eyes. If "E" is the

TABLE 5

FLUOROPHOTOMETER OUTPUTS AT VARIOUS FLASH INTENSITIES AND SLIT WIDTHS*

Flash Intensity Setting (slit width =0.2 mm)	Excitation Channel Output (V) (mean ± S.D.)	Concentration Output (V) (mean ± S.D.)	Deviation in Concentration Output from Grand Mean
1	0.184 ± .008	2.02 ± .02	1%
2	0.480 ± .012	2.00 ± .01	0%
3	1.03 ± .01	1.98 ± .01	−1%
4	1.76 ± .04	1.99 ± .01	−0.5%
Nominal Slit width (mm) (Flash intensity =2)			
0.05	0.0613 ± .0016	1.99 ± .04	−0.5%
0.1	0.206 ± .005	2.04 ± .02	2%
0.2	0.480 ± .012	2.00 ± .01	0%
Grand mean		2.00	

*Fluorescent glass standard, n=10.

TABLE 6

EFFECT OF EXTINCTION ON ACCURACY OF MEASUREMENTS OF FLUORESCEIN

Concentration Measurements				Mass Measurements			
True Concentration (g/ml)	Depth of Measurement (cm)	Measured Concentration	Error (%)	True Mass	Area of Distribution (cm^{2*})	Measured Mass	Error (%)
1×10^{-6}	0.1	$.98 \times 10^{-6}$	2	1×10^{-7}	0.4	$.97 \times 10^{-7}$	3
	0.2	$.96 \times 10^{-6}$	4		0.8	$.99 \times 10^{-7}$	1
	0.3	$.94 \times 10^{-6}$	6		1.2	$.99 \times 10^{-7}$	1
1×10^{-5}	0.1	$.80 \times 10^{-5}$	20	1×10^{-6}	0.4	$.77 \times 10^{-6}$	23
	0.2	$.64 \times 10^{-5}$	36		0.8	$.87 \times 10^{-6}$	13
	0.3	$.52 \times 10^{-5}$	48		1.2	$.91 \times 10^{-6}$	9

*Surface area of uniform distribution as "seen" by the fluorophotometer.

measured fluorescein concentration in the anterior chamber (the "error") immediately following iontophoresis of fluorescein into the cornea (before any significant mass of fluorescein could have entered the anterior chamber) and C_0 is the measured concentration of fluorescein in the portion of the cornea through which the beam passes when measuring anterior chamber concentration, the ratio $E{:}C_0$ is constant.

$$R = \frac{E}{C_0} \quad (3)$$

In the normal human eye, the value of R was small, .012 ± .004 (mean ± SD). If the value of R is measured for a given eye (by measuring E and C_0 immediately after iontophoresis), this value can be used to correct subsequent values of anterior chamber fluorescence. To use this correction, it is necessary to measure corneal fluorescein concentration, $C_0(t)$, each time anterior chamber measurements are made:

$$\text{corrected AC concentration} = \text{measured AC concentration} - R \cdot C_0(t) \quad (4)$$

A moderate degree of position sensitivity was found in the field of measurement of total mass. The excitation field in which mass measurement could be made is 9.5 mm in diameter for this instrument without additional modification. The excitation intensity was greatest in the center and weaker toward the edges of the field; the edge of the field was only 0.7 as sensitive as the center of the field, although the central 5 mm was fairly uniform. Thus, the calibration of mass and subsequent measurement of mass depends on its distribution. This finding led us to design our mass standard to be radially symmetrical with the solution deeper at the center than at the periphery.

The mass calibration experiment revealed that this standardization procedure was appropriate for a 4-mm centrally placed depot of fluorescein. The mean difference between the mass measurement and the true mass in the rabbit cornea was 1% ± 10% (mean ± SD) in the group of nine rabbit corneas tested. Furthermore, the mass measurement of these central corneal depots was not appreciably affected by changing the reflectivity of the surface behind the cornea. When the reflective surface equivalent to a dark brown human iris was changed to one equivalent to a light blue human iris, the mass reading was increased only 5%. This

finding indicates that the initial mass of a corneal depot can be measured with reasonable accuracy either in dark- or light-eyed subjects. This finding does not indicate that anterior chamber mass measurements would be similarly unaffected.

Discussion

The use of a xenon flash tube as the source of excitation for fluorescence has several advantages. First, it allows measurements to be made rapidly so that no appreciable eye movement can occur during the measurement. Second, it allows scaling of the photomultiplier light signal (for higher intensities of light) so that inadvertent entry of stray background light is well below the level at which photomultiplier tube damage can occur. Also, the tube can be protected with shutters that need to be open only for a brief period. Third, it reduces the relative effect of background illumination by increasing the intensity of the excitation light to much higher levels than can be tolerated by the subject from continuous light sources. These three advantages have the net effect of making the fluorophotometer convenient for clinical use.

The use of a matched photomultiplier tube to monitor excitation intensity would be a useful feature of any fluorophotometer. Variations in light intensity from the source or alterations in slit width will change the measured fluorescent signal, but can be compensated by an excitation monitor. Also, temperature-dependent and voltage-dependent changes in photomultiplier tube sensitivity tend to be minimized by measurement of excitation and fluorescent signals with matched photomultiplier tubes. This feature improves the stability of the fluorophotometer as compared to a single photomultiplier tube system.

The calibration tests indicate that fluorescein mass can be measured in the central cornea in subjects with dark or light irides. This finding does not indicate that total mass in the combined cornea and anterior chamber can necessarily be measured accurately when fluorescein is widely distributed in these two compartments. Many factors make such mass measurements uncertain, including lack of uniform fluorophotometer sensitivity in the field of measurement, obscuration of the peripheral cornea and anterior chamber by the corneoscleral limbal conjunctiva, and the intimate association between fluorescein and the irregular reflective surface of the iris stroma. However, several methods of measuring aqueous humor flow or corneal endothelial permeability to fluorescein do not require measurements of combined corneal and anterior chamber fluorescein mass,[6,14,15] although measurement of initial corneal mass ("dose") of fluorescein is an essential step in a newly described method (unpublished data).

The useful range over which fluorescein measurements can be made depends on the physical properties of fluorescein and the properties of the eye as well as the design of the fluorophotometer. Fluorescein, in high concentrations, attenuates the excitation beam, resulting in significant depression of fluorescence measurements. For concentration measurements, equation 2 can be used to predict the accuracy of a measurement made at any predetermined depth or to correct a measurement made at a known depth in a uniform solution of fluorescein. The effect of depth and concentration on measurements calculated from equation 2 are shown (Table 6). If the concentration in the excitation path does not exceed 10^{-6} g/ml, anterior chamber measurements can be made with reasonable accuracy without bothering to correct for extinction. Corneal measurements, made much nearer the surface, can be made at higher concentrations without correction.

Fluorescein mass measurements can be affected similarly. For corneal mass measurements, in which the fluorophotometer

excitation and observation axes are more nearly parallel, equation 2 cannot be applied directly, but must be integrated over the depth of the tissue. If the lateral distribution of fluorescein is uniform, the integrated form of equation 2 is applicable:

$$\frac{M'}{M} = \frac{[1 - e^{-\epsilon \cdot M/A}]}{\epsilon \cdot M/A} \quad (5)$$

where M' is the measured mass, M the true mass, M/A the mass per unit area as "seen" by the fluorophotometer, and ϵ the extinction coefficient. The effect of mass and distribution on the accuracy of fluorophotometric measurements is shown (Table 6). If the mass of fluorescein does not exceed approximately 10^{-6} g/cm^2 in the excitation field, reasonably accurate measurements of mass can be made without concern for the effects of extinction. Extinction thus places a practical upper limit on the concentration or mass that can be measured by fluorophotometry in the anterior segment of the eye.

The practical lower limit for concentration and mass measurements can be determined either by instrument sensitivity or by the level of background fluorescence and the intensity of stray light that passes through the barrier filter. The problem of instrument sensitivity is not the major factor with this instrument or with other instruments that have been described. With all instruments, the level of stray light can be lowered and instrument accuracy improved for measuring weak solutions of fluorescein by reducing background illumination to low levels.

One cannot eliminate, however, the background fluorescence of the ocular tissues or the tiny fraction of excitation light which, after scattering or reflection from the eye, is able to pass the barrier filter and excite the photomultiplier tube. Combining absorption and interference filters is helpful both for the excitation and the barrier filters. Additionally, one can measure the fluorescent signal of the eye before application of fluorescein and subtract this background signal from all subsequent measurements. This method is useful for corneal measurements, but practically unnecessary for anterior chamber measurements.

High concentrations of fluorescein in one area of the eye may affect measurements of low levels of fluorescence in another area of the eye. For example, if the excitation beam passes through a portion of the cornea containing ten times the fluorescein concentration of the anterior chamber, an error of more than 10% will be introduced into the measurement of anterior chamber fluorescence. The same phenomenon has been observed by Pederson, Gaasterland, and MacLellan,[16] who have suggested also that a correction be used.

Although there are limitations in the range of fluorescence that can be measured and precautions that must be observed in interpreting measurements, there is a broad range over which accurate measurements can be made simply. Other researchers have shown that fluorophotometry is a useful technique for studying the physiology of tear flow, corneal endothelial permeability, and aqueous humor flow.

For many clinical research studies, fluorescein measurement techniques have clear advantages, but remain largely unused. The use of a xenon flashtube as the light source for fluorophotometry allows the excitation beam to reach intense levels without bothering the subject. Consequently, measurements of fluorescence can be made rapidly and under lighting conditions customarily used in ophthalmic examination rooms.

SUMMARY

A new objective fluorophotometer measures fluorescein mass or concentration in the cornea or anterior chamber. The excitation source is a xenon flash

tube that allows the measurement of fluorescence to be made rapidly and conveniently. The instrument is designed for use in clinical studies requiring quantitative measurements of fluorescence in the tears, the cornea, and the aqueous humor.

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VITRECTOMY AND WAGNER'S VITREORETINAL DEGENERATION

GARY C. BROWN, M.D., AND WILLIAM S. TASMAN, M.D.
Philadelphia, Pennsylvania

First described by Wagner[1] in 1938, autosomal dominant vitreoretinal degeneration encompasses a multitude of ocular signs. Included in the original description are vitreous liquefaction and band formation, radial perivascular pigmentation, peripheral retinal pigmentation (probably lattice degeneration), peripapillary chorioretinal atrophy, narrow retinal arterioles, cataracts, myopia, and optic atrophy. Since that time, retinal breaks,[2–6] perivascular chorioretinal atrophy,[2] and white without pressure[3] have also been described. Retinal detachment is now recognized to be associated often with the disease and has been reported to be present in 47 to 67% of cases.[2–4] Redetachments following surgical repair are common.[2–6]

We describe herein three patients with Wagner's vitreoretinal degeneration who underwent vitrectomy, and suggest guidelines for vitrectomy as a therapeutic adjunct in the treatment of this disease.

CASE REPORTS

Case 1—A 14-year-old boy came to the emergency room April 12, 1976, with a history of loss of vision in the left eye of seven hours' duration. Aside from a -16.00 sphere refractive error in both eyes, the patient's history was noncontributory for eye disease. History of family ocular disorders included one sister with a retinal detachment and another sister with vitreous membranes and extensive peripheral retinal pigmentary changes.

Visual acuity at the time of examination was R.E.: 6/15 (20/50); L.E.: 6/60 (20/200). The anterior segments were noted to be normal bilaterally. Ophthalmoscopic examination of the right eye revealed equatorial lattice degeneration temporally. Examination of the left eye showed a bullous rhegmatogenous retinal detachment extending from the temporal periphery to the optic disk (Fig. 1). Vitreous bands were present, and the patient was thought to have Wagner's vitreoretinal degeneration.

Repair of the detached retina was undertaken on April 14 with scleral flaps, diathermy in a scleral bed, transscleral cryopexy, a silicone tire, an encircling band, and drainage of subretinal fluid. Subretinal fluid accumulation was minimal the first postoperative day, but had increased by the second postoperative day. This condition necessitated reoperation, at which time the original 8-mm implant was replaced with a 12-mm implant. Once again the retina was flat postoperatively, but redetached within three weeks. At this time there was apparent developing periretinal membrane formation. Revision of the scleral buckle was unsuccessfully attempted on May 28, 1976, and on June 5, the patient underwent pars plana vitrectomy with further revision of the scleral buckle. On most recent examination on Oct. 4, 1977, 16 months later, the visual acuity in the left eye was 6/30 (20/100), and the retina was flat (Fig. 2).

Case 2—An 11-year-old girl came here in February 1975 with a two-month history of decreasing

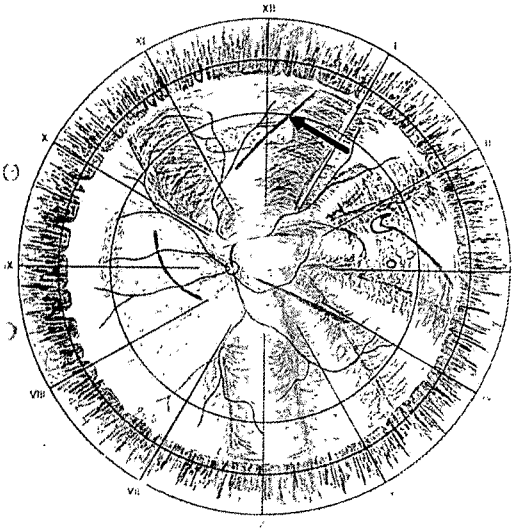


Fig. 1 (Brown and Tasman). Case 1. Initial examination. Rhegmatogenous retinal detachment with a horseshoe tear and two holes. Note the hypopigmented peripapillary and perivascular areas, perivascular pigmentary deposition, equatorial lattice degeneration, and vitreous bands (one of which is identified by an arrow).

From the Retina Service, Wills Eye Hospital and Research Institute, Philadelphia, Pennsylvania. This study was supported in part by the Retina Research and Development Foundation, Philadelphia, and the Lions Club of Pennsylvania.

Reprint requests to Gary C. Brown, M.D., Wills Eye Hospital, 1601 Spring Garden St., Philadelphia, PA 19130.

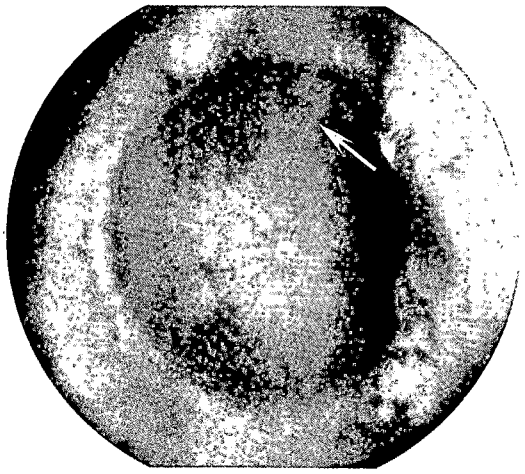


Fig. 2 (Brown and Tasman). Case 1. After vitrectomy. A remnant of one of the vitreous bands (arrow) cut during surgery is seen in this wide-angle photograph.

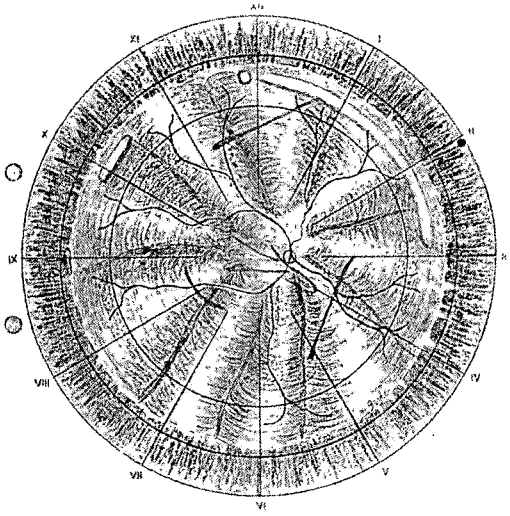


Fig. 3 (Brown and Tasman). Case 2. Initial examination. Bullous total retinal detachment with two tears and a hole. Vitreous bands and pigmentary changes, as in Case 1, are present.

vision in the right eye. At 5 years of age she had had rapidly decreasing vision in the left eye, the cause of which was undetermined. Family history revealed her mother had decreased vision bilaterally secondary to retinal detachments, and her two brothers had retinal detachments. Several aunts and uncles had histories of impaired vision, the causes of which were unknown.

Examination on Feb. 25, 1975, revealed the visual acuity to be R.E.: finger counting at 6 ft; L.E.: no light perception. Refractive error in the right eye was a −11.50 sphere. Refractive error in the left eye was unobtainable because the eye was phthisical with band keratopathy. The anterior segment of the right eye demonstrated 1+ flare and cells, but otherwise was within normal limits. Ophthalmoscopic examination disclosed a total retinal detachment with a 90-degree superonasal giant tear and a 20-degree superotemporal tear (Fig. 3). Equatorial and perivascular pigmentary changes were noted, and vitreous bands were present. Because of these findings and the family history, the patient was thought to have Wagner's vitreoretinal degeneration.

Repair of the detached retina was attempted with scleral flaps, diathermy to the bed, a silicone plate, an encircling band, and drainage of subretinal fluid. Fluid remained inferiorly postoperatively, and by April 2, 1975, the retina had again detached totally with apparent massive periretinal proliferation. A second attempt at repair was made on April 8 by using a scleral bed with cryotherapy, an encircling band, and subretinal fluid drainage, but apparent massive periretinal proliferation remained (Fig. 4). On May 19, the patient underwent combined lensectomy and open-sky vitrectomy. An 8.5-mm corneal button was removed at the start of the procedure and was replaced upon termination of the vitrectomy. On follow-up examinations, the retina has remained flat (Fig. 5), but the visual acuity was, disappointingly, hand motion when the patient was last seen in March 1977.

Case 3—A 3-year-old girl was examined by her primary ophthalmologist on April 26, 1976, because

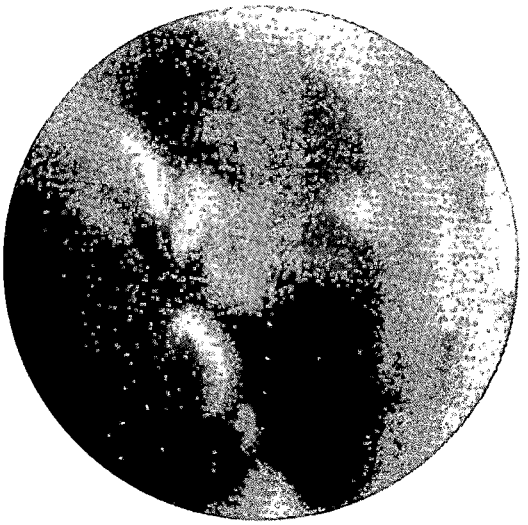


Fig. 4. (Brown and Tasman). Case 2. Previtrectomy. Fundus as it appeared after the second unsuccessful retinal detachment repair. The picture is that of apparent massive periretinal proliferation.



Fig. 5 (Brown and Tasman). Case 2. After vitrectomy. Two of the smaller vitreous bands (arrows) still remain. The retina was flat at this time and had remained so at the 22-month follow-up examination.

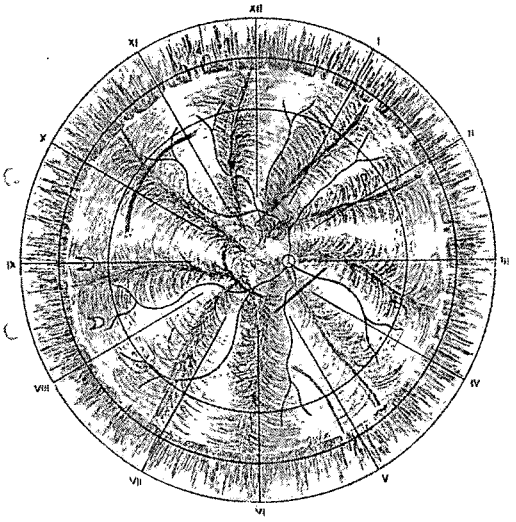


Fig. 6 (Brown and Tasman) Case 3. Fundus on initial examination revealing a bullous total retinal detachment with two nasal horseshoe tears. Equatorial lattice degeneration and vitreous bands are present, as in the other cases.

of parental concern over the progressive darkening in color of her right iris. Ocular examination confirmed this finding and also revealed the presence of a cataract and total retinal detachment in the right eye. The patient was admitted here, where examination under anesthesia on April 29 confirmed the presence of a posterior subcapsular cataract and a total retinal detachment with two nasal horseshoe tears in the right eye (Fig. 6). A −8.00 sphere refractive error was noted in the left eye, and vitreous bands were present in both eyes. Ophthalmologic examination of family members revealed her father and a paternal aunt and uncle to have findings classic for Wagner's vitreoretinal degeneration.

On May 3, repair of the detachment was attempted with scleral flaps and a silicone tire, transscleral cryotherapy, an encircling band, and subretinal fluid drainage. A small amount of subretinal fluid remained, but on May 10, examination under anesthesis once again disclosed a bullous total retinal detachment in the right eye with massive periretinal proliferation. The patient underwent revision of the scleral buckle, lensectomy, and pars plana vitrectomy on June 28, 1976. The retina remained flat on most recent examination in June 1977.

Discussion

Prognosis for successful reattachment of the retina in Wagner's disease is poor. Hirose, Lee, and Schepens[3] reported 17 (52%) of operated eyes to be detached at six months in their series of 33 eyes. Additionally, of those eyes undergoing three or more retinal detachment repairs, only three of ten (30%) remained attached. Hagler and Crosswell[2] had surgical failure in 36% of the eyes of their series of 22 patients with perivascular chorioretinal degeneration, myopia, presenile cataracts, and vitreous veils.

Vitrectomy has been reported to be of therapeutic value in patients with retinal detachment and vitreous bands,[7–11] but to our knowledge, there have been no reports of this procedure being used specifically for Wagner's disease. Vitrectomy seems to be a therapeutic adjunct following unsuccessful retinal detachment repair using conventional scleral buckling and encircling techniques. The retinas of our three patients have now remained attached for 16, 22, and 12 months, respectively, after vitrectomy. The patient in Case 1 underwent three unsuccessful retinal detachment procedures before successful vitrectomy, whereas the patient in Case 2 underwent attempted repair twice, and in Case 3, once.

At no time in these cases was membrane stripping attempted, although the fundus pictures suggested massive periretinal proliferation. The majority of the gel was removed with the intravitreal bands. We believe that these bands are vitally important in the production of retinal detachment associated with Wagner's disease. In our cases, they may also have been partially responsible for the appearance of apparent massive periretinal proliferation after unsuccessful retinal detachment repair. Removal of the bands may explain successful reattachment of the retinas.

Whereas scleral buckling and encircling band procedures comprise initial management, vitrectomy should be considered in the therapeutic regime, especially in reoperative procedures.

SUMMARY

A 14-year-old boy, an 11-year-old girl, and a 3-year-old girl with Wagner's vitreoretinal degeneration had multiple retinal detachments. Surgical repair by means of conventional scleral buckling and encircling techniques was unsuccessful. However, after vitrectomy, their retinas remained flat.

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A COMPARISON OF THE EFFECTS OF TIMOLOL AND EPINEPHRINE ON INTRAOCULAR PRESSURE

ALAN P. MOSS, M.D., ROBERT RITCH, M.D., NEWELL A. HARGETT, M.D., ALAN N. KOHN, M.D., HARRY SMITH, JR., PH.D., AND STEVEN M. PODOS, M.D.
New York, New York

The ocular hypotensive properties of the beta-adrenergic blocking agents have been recognized since 1967, when it was noted that oral propranolol decreased the intraocular pressure.[1] Subsequent studies showed similar agents, such as oxprenolol,[2] pindolol,[3] atenolol,[4-6] and practolol[7] to be effective in decreasing intraocular pressure when administered either systemically or topically. Some of these drugs, however, have been associated with severe adverse side effects.[8-14]

Timolol maleate, another beta-adrenergic blocking drug, has shown impressive ocular hypotensive effects without significant ocular or systemic side effects.[15-21] Timolol decreased intraocular pressure both in normotensive patients[15] and, as compared to a placebo,[17,18] in patients with open-angle glaucoma. Short-term studies[18] have demonstrated that 0.5% timolol solution is at the peak of the dose-response curve. At this concentration, ocular hypotensive effects were noted for 24 hours or longer. The mechanism of the ocular hypotensive effect has not been fully elucidated, but studies[16] have suggested effects on the production of aqueous. Moreover, timolol appeared to be as effective as pilocarpine or epinephrine,[19,21] and its effect was additive to these commonly used compounds.[20]

We compared the effects of timolol maleate and epinephrine hydrochloride in patients with ocular hypertension or open-angle glaucoma.

SUBJECTS AND METHODS

Sixteen patients with primary open-angle glaucoma and 20 patients with ocular hypertension were examined in a double-masked crossover study (Table 1). Patients were considered to have primary open-angle glaucoma if their intraocular pressures when not taking medications were measured as ≥22 mm Hg by Goldmann applanation tonometry, and there was coexisting characteristic abnormality in the visual field, optic nerve head, or both. Ocular hypertension was defined as untreated intraocular pressure of ≥25 mm Hg, without either of these coexisting changes. Although the eyes of each patient were treated identically, two open-angle glaucoma patients qualified by these criteria in one eye only. For the purposes of data analysis, only the glaucomatous eye was considered. Patients were excluded if they had had intraocular surgery, severe ocular trauma, dendritic keratitis, or active corneal ulcer within the previous three months. Also excluded were patients with secondary glaucoma, including glaucoma resulting from trau-

From the Department of Ophthalmology, Mount Sinai School of Medicine of the City University of New York, New York. This study was supported in part by grant EY-02514 and by fellowship grant EY-05128 from the National Eye Institute, National Institutes of Health, Bethesda, Maryland (Dr. Ritch); Fight for Sight fellowship grants F-304 (Dr. Moss) and F-302 (Dr. Hargett); an Earl Wilson Award (Dr. Moss) and Elsie K. Sloate Award (Dr. Hargett) from Fight for Sight, Inc.; and by Merck Sharpe and Dohme Research Laboratories. Dr. Ritch was a Heed Foundation Fellow (1976-1977); Dr. Cohen was a Heed Foundation Fellow (1977-1978).

Reprint requests to Robert Ritch, M.D., Department of Ophthalmology, Mount Sinai School of Medicine of the City University of New York, Fifth Ave. and 100th St., New York, NY 10029.

TABLE 1

CHARACTERISTICS OF THE STUDY POPULATION

	Open-Angle Glaucoma	Ocular Hypertension
Age		
Mean yrs	59.9	63.3
Range in yrs	30-82	42-77
Sex		
Male	10	11
Female	6	9
Race		
White	10	13
Black	5	5
Hispanic	1	2
Signs		
Altered visual field and optic nerve	10	—
Altered visual field	1	—
Optic nerve changes	5	—
Neither visual field nor optic nerve changes	—	20

matic angle deformity, corneal abnormalities preventing reliable applanation tonometry, history of retinal detachment, diabetic retinopathy, or any other potentially progressive retinal diseases, and pregnancy or potential pregnancy among women not using adequate contraceptive methods.

After a one-week washout period with no glaucoma medication, patients returned for a baseline examination. A second week of washout before baseline was carried out if the intraocular pressure remained too low to qualify for inclusion in the study. Patients who qualified were then randomly assigned, according to a computer-generated random numbers table, to begin receiving either timolol maleate or epinephrine hydrochloride. Dosages were adjusted on weekly return visits with coded bottles of ascending concentrations of timolol maleate solution twice a day (0.1%, 0.25%, 0.5%) or epinephrine hydrochloride solution twice a day (0.5%, 1.0%, 2.0%) in both eyes.

Patients were arbitrarily judged to be adequately controlled if, on each of two measurements 30 minutes apart with a Goldmann applanation tonometer, the intraocular pressures of both eyes were ≤21 mm Hg or when intraocular pressures were ≤25 mm Hg and the investigator believed the patient was having an adequate clinical response. Examinations were performed at approximately the same time of day for each patient to minimize the effects of diurnal variation on intraocular pressure. The controlled patients continued in a six-week maintenance portion of the study. Uncontrolled patients and patients completing the maintenance period were then crossed over into the second treatment period with the other drug, preceded by a second washout period of one week.

During the second treatment period, the second drug was titrated in patients at weekly dose adjustment visits. Those patients who were controlled entered into a six-week maintenance period. Patients completed the study when control was no longer possible or on concluding this maintenance period.

During each examination the visual

acuity, intraocular pressure, pupil size, slit-lamp observation, pulse, and blood pressure were recorded. Patients were also questioned as to subjective side effects. During baseline, washout, and final examination for each treatment, visual field, tonography, Schirmer test, and ophthalmoscopic examinations were performed.

RESULTS

Ten of 19 patients receiving epinephrine hydrochloride and 14 of 17 patients receiving timolol maleate were controlled during the first treatment period (chi-square not significant). Overall, the intraocular pressure of 17 patients was controlled by both drugs. Timolol, but not epinephrine, was effective in ten patients. Epinephrine, but not timolol, was effective in two patients. Four patients could not be controlled by either drug, and three patients did not complete the study. The number of patients controlled with the various concentrations for each study drug is shown (Table 2). The total of 30 of 36 patients controlled with timolol was significantly greater than the 19 of 33 controlled with epinephrine ($P<.025$).

For the first treatment period, mean baseline intraocular pressures were virtually identical (28.9 ± 0.6 mm Hg for patients initially taking epinephrine and 28.3 ± 0.8 mm Hg for patients initially taking timolol). The second washout period constituted the baseline for the second treatment period. The mean washout intraocular pressure for those patients discontinuing timolol and about to begin epinephrine was 23.1 ± 0.8 mm Hg. The mean intraocular pressure for those patients discontinuing epinephrine and about to begin timolol was 26.0 ± 0.7 mm Hg. This difference was not statistically significant.

The mean decrease in intraocular pressure was significantly greater both for the first treatment period alone and for the study overall at both the lowest ($P<.05$) and highest ($P<.005$) concentration of drug used (Table 3). No tachyphylaxis was noted for either drug during the six-week maintenance period. Three patients receiving epinephrine and one patient receiving timolol did require one dose readjustment each and reentry into the maintenance period when a low concentration of drug failed to maintain effective control after initial entry into the maintenance period. There was no significant difference in response to either drug between whites and nonwhites or between open-angle glaucoma patients and ocular hypertensives.

Among other factors observed, only pupil size showed any significant alteration for either drug. The mean pupil size of 3.8 ± 0.1 mm in patients receiving epinephrine was significantly larger than the baseline 3.3 ± 0.2 mm ($P<.05$). The

TABLE 2

DISTRIBUTION OF PATIENTS CONTROLLED OR IN WHOM DRUG WAS INEFFECTIVE ACCORDING TO STUDY DRUG CONCENTRATION AND STUDY PERIOD

	Initial	Crossover	Total
Epinephrine			
Effective			
0.5%	5	4	9
1.0%	4	4	8
2.0%	1	1	2
Total	10	9	19
Ineffective	9	5*	14*
Timolol			
Effective			
0.1%	6	11	17
0.25%	3	2	5
0.5%	5	3	8
Total	14	16	30
Ineffective	3	3	6

*Three additional patients were lost to follow-up during crossover period.

TABLE 3

MEAN DECREASE IN INTRAOCULAR PRESSURE AT THE LOWEST AND HIGHEST CONCENTRATIONS OF THE STUDY DRUGS

	Decrease in IOP (Mean mm Hg ± SE)				
	Before Crossover	No. of Patients	After Crossover*	No. of Patients	Total
Lowest concentration					
Epinephrine	4.9 ± 0.2	(19)	3.0 ± 0.2	(17)	4.0 ± 0.2
Timolol	6.9 ± 0.2†	(17)	5.6 ± 0.2†	(19)	6.3 ± 0.1‡
Highest concentration					
Epinephrine	6.9 ± 0.2	(19)	4.1 ± 0.2	(17)	5.1 ± 0.1
Timolol	8.6 ± 0.2†	(17)	6.7 ± 0.2†	(19)	7.7 ± 0.1§

*Designates from crossover washout baseline.
Significant difference between patients tested with epinephrine and those tested with timolol, Student-t test: †P<.05
‡P<.01
§P<.005.

mean pupil size of 3.5 ± 0.1 mm in patients receiving timolol did not differ significantly from that of the patients taking epinephrine or from baseline. No significant alterations during the study were found for visual acuity, applanation tonography, Schirmer test, visual field, optic nerve head pulse, and blood pressure. Adequate data on applanation tonography and Schirmer testing were available, however, for only 19 and 12 patients, respectively.

Four adverse reactions required cessation of administration of the study drug during the epinephrine treatment period: (1) headache and burning, (2) blurred vision, (3) blepharoconjunctivitis, and (4) palpitations (Table 4). An additional patient stopped taking epinephrine when he was hospitalized with a myocardial infarction. Patients taking timolol had no significant adverse side effects.

DISCUSSION

This double-masked crossover comparison study demonstrated timolol to be an effective ocular hypotensive agent. Most patients took the drug throughout both a

TABLE 4

RECURRENT MINOR ADVERSE SIDE EFFECTS

	No. of Patients	
	Epinephrine	Timolol
Subjective		
Burning, smarting, soreness, or headache	7	5
Dryness, foreign body sensation, or tearing	1	2
Blurred vision	3	0
Itching	1	0
Objective		
Conjunctival hyperemia	3	5

three-week dose adjustment and a six-week maintenance, without adverse ocular or systemic side effects. No evidence of tachyphylaxis was noted during this length of time.

The epinephrine salts have long been a mainstay in the treatment of glaucoma.[22] Timolol was both more effective in decreasing intraocular pressure and better tolerated than epinephrine hydrochloride at the concentrations used in this study. The maximum ocular hypotensive effect of either drug, however, was not analyzed because of the design of the study.

Of 36 patients in the study, 17 were controlled with 0.1% timolol, the lowest concentration used. This could suggest that 0.1% timolol approaches the peak of the timolol dose response curve for many patients. An alternative explanation, however, might be that the arbitrary end point of control of 22 mm Hg or less, established for drug titration in this study, could have resulted in many submaximal responses to timolol. The findings of Zimmerman[18] that 0.5% timolol appeared to yield the maximal ocular hypotensive effect supports the latter interpretation. Conversely, only nine patients were controlled by the lowest concentration (0.5%) of epinephrine, with ten additional patients controlled by 1.0% or 2.0%. Since the drug was titrated in all patients until controlled, or until the drug was found to be ineffective, most patients received 1.0% or 2.0% epinephrine. Dose-response investigations for epinephrine have shown that maximum responses are generally achieved with the 1% solution, with slight additional efficacy at the 2% concentration.[23–26] Thus, patients more likely demonstrated a near-maximal response to epinephrine than to timolol at the concentrations used during this study.

Significant changes in outflow facility were not noted with timolol, which confirmed previous findings.[16] Yablonski[27] showed by fluorophotometry that the ocular hypotensive effect of timolol could be accounted for by reduced production of aqueous. Previous studies have shown that enhancement by epinephrine of outflow facility occurs with 1% or greater concentrations,[23,24] used over extended periods[28,29] in patients with glaucoma.[30] These studies are inconsistent.[30–32] In our study, we noted no significant effect of epinephrine on facility of outflow.

No effects of timolol on pupil size, visual acuity, pulse, or blood pressure were found, which confirmed previous reports.[15,17–19]

None of the patients had any severe adverse reactions while taking timolol, which agreed with earlier studies.[15–19] In contrast, a number of patients (four of 36) were unable to tolerate epinephrine during the relatively short period of our study. The adverse reactions were typical of those known to limit patient tolerance to epinephrine.[22] Only a few patients voiced complaints or showed signs of minor irritation with either drug.

Untoward side effects, including various cutaneous eruptions, have been noted with systemic oxprenolol[13,14] and propranolol.[12] Topical propranolol could not be used for chronic treatment of glaucoma because of its local anesthetic effects. Adverse reactions to other beta-blocking agents have been widely reported in previous studies. The oculomucocutaneous syndromes and sclerosing peritonitis associated with the systemic administration of practolol are the most serious adverse reactions and are thought to have an autoimmune basis.[8–11]

Little research has been done on practolol as a topically applied ocular hypotensive agent.[7] Such adverse reactions have not been reported with any of these agents when administered topically to the eye.[5–7] There were no significant changes in Schirmer test or in rose bengal staining

during our study; however, Mackie, Seal, and Pescod[33] pointed out that these are insensitive indices of tear flow. A more sensitive sign of dysfunction, such as tear lysozme concentration[33] or tear flow fluorophotometry,[34] may be helpful during future clinical studies.

SUMMARY

We conducted a double-masked, six-week crossover study comparing bilateral twice-a-day therapy with timolol maleate (0.1%, 0.25%, and 0.5%) and epinephrine hydrochloride (0.5%, 1.0%, 2.0%) in 36 otherwise untreated patients. Increasing concentrations of each drug were administered until an arbitrary level of control was achieved before each of the six-week follow-up periods.

Seventeen patients were controlled by both drugs and four patients were controlled by neither drug. Timolol, but not epinephrine, was effective in ten patients, whereas epinephrine, but not timolol, was effective in two patients. Three patients did not complete the study. The mean decrease in intraocular pressure from baseline was significantly greater with timolol than with epinephrine both before crossover and overall at both the lowest and highest concentrations of drug used. Significant toxicity was produced in four patients during treatment with epinephrine, but in no patients during treatment with timolol.

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MEDICOLEGAL HAZARDS OF INTRAOCULAR LENS IMPLANTING

JEROME W. BETTMAN, M.D.
Woodside, California

The number of intraocular lens implants (IOL) has increased such that the procedure can no longer be considered experimental. In one year, some 3,000 ophthalmologists implanted approximately 75,000 lenses.[1] There are nevertheless associated medicolegal hazards that do not exist to the same degree with other procedures. The safety and efficacy of intraocular lenses have yet to be established. A study to determine this, funded by the National Eye Institute, is under way. Special requirements of the Food and Drug Administration governing investigational devices must be met.[2]

The number of medicolegal claims filed by patients who have had implants is increasing because more surgeons are using more implants. The time interval between the alleged act of malpractice and the trial is so long that years must elapse before the number of claims can be estimated. In San Francisco the average time between the alleged substandard act and the trial is now five years. I speculate that the number of claims based on lens implants will be large within a few years. My series of cases of "malpractice" suits in ophthalmology now stands at 275. Two years ago, when this series was almost 200, it included no claims related to intraocular lenses; one year ago there were two; now there are ten, and I am aware of 16 more.

I believe that there are reasons why there is an unusual risk of litigation with IOL implanting, and special precautions should be taken to minimize the risk.

I will not discuss the customary precautions that may be taken to avoid litigation in the ordinary case without implant. This has been extensively discussed.[3]

The following produce an increased hazard of litigation: (1) publicity; (2) an unfavorable risk:benefit ratio in many cases; and (3) special problems related to informed consent and, as a part of this, diminished opportunity to establish rapport between ophthalmologist and patient.

Intraocular lens implants, an exciting, new, and appealing development in cataract surgery, have and will continue to generate more publicity in the lay media than more mundane operations. The publicity is frequently inaccurate, and if it is more favorable than the facts justify, a patient will expect that a good result is routine and may sue if it is not. Unfavorable publicity may cause the patient with a poor result to ask why his surgeon subjected him to the jeopardy of this procedure, even if the patient requested it.

Publicity has encouraged a large number of patients to ask the ophthalmologist to put in an implant. Many surgeons have felt the pressure to put in an implant against their own judgment. Some have undertaken the operation because of fear of losing the patient if they refused. Among this group are some with inadequate skill or insufficient training.

The risk:benefit ratio is often unfavorable. Consider the patient with preoperative visual acuity of 6/18 (20/60) in one eye and 6/6 (20/20) in the other. If all goes well, his vision is moderately improved. If problems arise, the 6/18 (20/60) eye may become an implanted 6/120 (10/200) eye. The patient will be unhappy. If rapport, informed consent, and other preliminaries were inadequate, the patient may

From the Departments of Ophthalmology, Pacific Medical Center, San Francisco; University of California, San Francisco; Stanford University; Stanford, California.

Reprint requests to Jerome W. Bettman, M.D., 3910 Sand Hill Rd., Woodside, CA 94062.

be angry; and unhappy, angry patients frequently sue. This is not just a theoretical situation.

My series included 275 cases of litigation in ophthalmology, in 60 of which cataract operations were the primary problem. Ten had intraocular lens implants. Another group had extenuating reasons for litigation and probably would have sued regardless of the preoperative vision. These were eliminated from further consideration and included cases of cataracts induced by drugs, toxins, or radiation; eyes damaged by chemical burns, contact lenses and the like; congenital cataracts; and endophthalmitis.

There were some in which the preoperative vision could not be ascertained. There remained 13 without extenuating reasons for litigation, in whom no implant had been inserted. The preoperative vision is shown (Table 1). Only one of the 13 patients had visual acuity in the better eye of less than 6/18 (20/60). Obviously, these patients had more to lose than individuals whose vision in the better eye was poor. The preoperative visual acuity in the ten intraocular implant cases that came to litigation is shown (Table 2). None of the patients had visual acuity of less that 6/18 (20/60) preoperatively. This suggests that patients with relatively good vision preoperatively are more inclined to sue than those with poor vision.

One of the more common indications for lens implants is good vision of one eye. Even the visual acuity in the eye to be implanted is not too bad in a number of cases. Gentry[4] lists the preoperative as well as the postoperative vision in the implanted eye in 100 patients. Thirty of the 100 had preoperative visual acuity of 6/18 (20/60) or better. One would presume that the visual acuity in the other eye was better than that in the implanted eye, in most cases. This is not a favorable risk:benefit ratio. The anlage for litigation is present and, if the surgical result is not good, beware.

The circumstances were different before we had the pseudophakos to offer the patient. The surgeon was less willing to operate on a patient with one good eye because of the obvious difficulties in attaining binocularity and because of uncertainty that the patient could, or would, wear a contact lens. The deterrent was removed with the advent of the pseudo-

TABLE 1

PREOPERATIVE VISUAL ACUITY IN 13 CASES OF CATARACT PATIENTS WITHOUT IOLS THAT CAME TO LITIGATION

Patient No.	Age (yrs)	Visual Acuity R.E.	Visual Acuity L.E.
1	57	6/6 (20/20)	6/12 (20/40)
2	71	6/15+ (20/50+)	6/6 20/20)
3	66	6/30 (20/100)	6/6 (20/20)
4	73	6/9+ (20/30+)	6/24 (20/80)
5	82	6/7.5 (20/25)	Finger counting – 15'
6	80	6/60 (20/200)	6/7.5 (20/25)
7	56	6/7.5 (20/25)	6/30 (20/100)
8	63	Finger counting	6/6 (20/20)
9	Not obtained	6/15 (20/50)	6/18 (20/60)
10	69	6/30 (20/100)	6/30 (20/100)
11	50	6/6 (20/20)	6/60 (20/200)
12	Not obtained	6/60– (20/200–)	6/6 (20/20)
13	46	Hand motions	6/15 (20/15)

TABLE 2

VISUAL ACUITY IN TEN IOL CASES THAT CAME TO LITIGATION

Patient No.	Age (yrs)	Preoperative Visual Acuity		Postoperative Visual Acuity With IOL	
		R.E.	L.E.	R.E.	L.E.
14	68	6/9−2 (20/30−2)	6/60 (20/200)	Not operated	6/30 (20/100)
15	59	6/12 (20/40)	Unknown	Not operated	6/120− (20/400−)
16	63	Unknown	6/9 (20/30)	6/60 (20/200)	Not operated
17	77	6/18 (20/60)	6/60 (20/200)	6/6 (20/20) without IOL	6/24 (20/80)
18	75	6/9 (20/30)	6/60+2 (20/200+2)	Not operated	"Unimproved"
19	81	Unknown	6/24 (20/60)	<6/60 (<20/200)	6/4.5 (20/15)
20	64	6/30 (20/100)	6/7.5 7.5 (20/25)	6/12 (20/40)	Not operated
21	84	6/60 (20/200)	6/9 (20/30)	6/12 (20/40)	Not operated
22	54	6/6 (20/20)	Unknown	Not operated	Hand motions
23	70	6/12− (20/40−)	6/22 (20/70)	Not operated	6/6/ (20/200)

phakos. Possibly a new deterrent, the threat of litigation, is being substituted.

Informed consent is even more important in implant cases than in most others. The use of an implant is an elective procedure, and in all elective procedures, the need for fully informed consent is much greater than in others. The importance of informed consent is further amplified by the common situation in which the implant surgeon is busy and has little time to build a rapport with the patient. These patients are frequently referred to him and are seen for only a short period before and after the operation.

The incidence of suits against chiropractors is not high. The chiropractor has little to sell except his rapport with the patient. The rapport is enhanced by time spent in manipulation and conversation. The chiropractor's knowledge and therapeutic ability may leave much to be desired, but he rarely gets sued. The implant surgeon is in an opposite position.

The methods of conveying information basic to consent may be written or verbal. Because of the unusual risk, both should be used.

A written form should be developed for implants, although I am not always in favor of them for all procedures. Verdicts based on informed consent theoretically should be nonexistent because it is something that the surgeon can protect against in advance, unlike many medical complications. Yet the perfect form has not been devised. I have solicited the opinions of several excellent attorneys who only practice medicolegal defense. Their opinions vary enormously. I shall not attempt to offer a model form, but will submit guidelines that are distilled from a number of opinions.

There are two fundamentals: (1) All significant information must be conveyed so that the patient understands, and the surgeon should be reasonably certain that he does understand. This requires feedback in the form of verbal communication. The test as to whether the information should be conveyed is whether or not a prudent person, if informed of the given risk, might be influenced in his decision. (2) Evidence that the patient was informed must be documented in such a way that the patient cannot deny it. Generally, it is wise to keep the disclosure simple, but to cover the more common and serious problems in general terms. I would include the following information: (A) The procedure is new, although not experimental. Long-term hazards may exist of which we are unaware. (B) The risk of complications is greater than with a cataract without implant. Although there are advantages, there are also greater

perils, such as hemorrhage, infection, the need for additional operations, and diminished or even complete loss of vision. Special risks known to be associated with certain types of pseudophakos should be presented.

It is wise to include the possibility of blindness in the eye because if a prudent person accepts this risk, he can hardly maintain that he would have refused the procedure because of a significantly lesser complication.

The risk of anesthesia should be included, even the rare possibility of death, but mentioning death does not absolve the surgeon of other risks. Death is not a realistic peril to most people, and the patient will say that the possibility was too remote to influence him, although other complications did.

In reading several standard consent forms for lens implanting, I have been disturbed that some did not indicate that the risk was greater with implants than with the ordinary cataract. Because standard complications, for example, hemorrhage, infection, and the like, are presented, this does not convey the possibility of added risk. The patient may, and in some instances has, used this as a complaint.

(C) One should clearly explain that foreign material is implanted, and that there is need for prolonged medication.

(D) The patient must understand that the surgeon may decide not to implant a pseudophakos. The surgeon must have the freedom to abort the procedure, if indicated. Patients have sued because of failure of implantation.

Some attorneys think that the disclosure should include the approximate incidence in percentages of the more common risks, but others disagree. The argument in favor of including them is that the plaintiff might say that the complication was mentioned, but he had no idea it was that common. Conversely, if the percentages are specified, the actual incidence may differ substantially from the given figure. This could be difficult. I give an indication of incidence without stating figures.

If a printed form or a routine taped message is to be used, the form or tape must be properly done, or it can be incriminating. It is unwise for a surgeon to write such a form or dictate such a tape without good legal advice, which should be obtained from an attorney experienced in the defense of physicians. Such an attorney may be found through the guidance of medical societies. There are forms available through the Implant Society and other sources. These are helpful as a basis, but modification with the help of an attorney may be desirable.

The form should be signed by the patient, spouse, office nurse, or all three, but only after verbal communication has indicated that the patient does understand what he has read or heard. It is well to ask questions of the patient to determine his understanding (feedback). The verbal portion should be done by the surgeon, not a receptionist, nurse, or even the assistant surgeon.

Ideally, the verbal portion of the informing process should start before the consent form is used. It is usually wise to talk to the patient about your own thinking in the decision-making process as the advantages and disadvantages are weighed. Keeping the patient fully informed, leveling with him at all times, can be an important factor in the prophylaxis of suits for alleged malpractice.

One may have the patient listen to a tape instead of reading the printed form. The creation of the tape requires all of the careful planning that the printed form does, but has a disadvantage: the patient cannot sign it. Even if he signs a statement that he heard and understood the tape, he may later maintain that it was not that tape, or that part was missing or

inaudible. Movies or brochures that explain the procedure have a similar disadvantage. The patient may allege that it was not that movie or brochure which was presented to him.

One can tape the verbal information as it is being conveyed to the patient, such as, "I am speaking to Mr. Jones about his operation which is scheduled for . . . ." After conveying the information, the microphone can be handed to the patient for his feedback. This has the advantage that the patient's voice is recorded as a documentation, but there are two disadvantages: (1) if it is not done right, it can be used as evidence against the surgeon; (2) numerous tapes can be expensive, and storage may be a problem.

Whatever method is used should not be so cumbersome as to make it unfeasible.

A printed form, properly constructed for the surgeon's needs, used with verbal communication, and signed by the patient and a witness is probably the best method of obtaining informed consent for the implant operation.

What may be an adequate method of informed consent for the established leaders in the field may not be adequate all surgeons. Surgeons such as Jaffe, Kratz, Galin, and others of their experience, have set the standard. Therefore, it is difficult for the plaintiff to maintain that their procedure is below standard, a synonym for malpractice, because their actions are the standard. Such is not the case with the average surgeon, and he is at greater risk of litigation.

Informed consent should be obtained before the patient is hospitalized. If not, the patient may claim that the confusion of registering, preliminary tests, and medications made it impossible for him to understand clearly.

There are special medicolegal hazards associated with the use of the pseudophakos, but those hazards can be minimized if the surgeon does not operate on a patient who does not have a significant visual handicap, and if he uses a well-planned method of obtaining informed consent and documents it.

The procedures important to diminish the possibility of litigation in all of medicine are no less important here. These include attaining competence in the given procedure, keeping good medical records, using consultants whenever indicated, and, above all, always maintaining good rapport with the patient.

SUMMARY

If the result of cataract extraction is not good, patients with relatively good preoperative vision are more likely to sue than those with poor preoperative vision. One of the usual indications for use of a pseudophakos is good vision in one eye. At times the preoperative acuity in the operated eye is not bad. This creates an unfavorable risk:benefit ratio. Other factors that add to the risk of litigation are publicity in the lay press and problems with properly informing the patient to obtain consent.

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THE INCIDENCE OF HLA ANTIGENS IN BLACK PRIMARY OPEN-ANGLE GLAUCOMA PATIENTS

JUNE FORE SHAW, M.D., RALPH Z. LEVENE, M.D., AND JOHN G. SOWELL, PH.D.
Birmingham, Alabama

Many associations between HLA antigens and diseases have been reported and the most comprehensive compilation and interpretation of the data is in HLA and Disease.[1] Only a few ophthalmic diseases have exhibited a positive association with an HLA antigen to the degree of statistical conformity required by the HLA and Disease Registry: acute anterior uveitis, optic neuritis, Harada's disease, Behçet's disease, and retinoblastoma.[1] The glaucoma data submitted for joint analysis to the First International Symposium on HLA and Disease (Paris, 1976) were derived from one Japanese and three white populations, two of the latter originating in the United States. According to the Registry analysis, the submitted data showed no statistically significant association between the HLA antigens and glaucoma.[1] Eight publications from two institutions in the United States claim that HLA antigens are positively associated with glaucoma.[2-9] One[6] claims a statistically significant increase in HLA-B7 and HLA-B12 in a black glaucoma population; another,[8] a decrease in HLA-A1 and HLA-A11 in black glaucoma patients.

In an effort to confirm these claims, we undertook this study to compare the HLA antigen frequencies in black primary open-angle glaucoma patients to those in: (1) black nonglaucomatous patients; (2) normal, nondiseased black individuals; and (3) a control group of nondiseased North American blacks[10] (Sixth International HLA Workshop data).

From the Departments of Pathology (Dr. Shaw) and Ophthalmology (Drs. Levene and Sowell), University of Alabama School of Medicine and the Eye Foundation Hospital, Birmingham, Alabama. This study was supported in part by grant No. EY01536-04 from the National Eye Institute (Drs. Levene and Sowell).

Reprint requests to June Fore Shaw, M.D., Department of Pathology, University of Alabama School of Medicine, 619 South 19th St., Birmingham, AL 35294.

SUBJECTS AND METHODS

Selection of populations—Forty-eight black primary open-angle glaucoma (POAG) patients were randomly chosen for HLA typing from the ophthalmology clinic of the Eye Foundation Hospital. All patients had untreated intraocular pressures greater than 21 mm Hg and characteristic glaucomatous field changes. The male:female ratio of this population was 19:29; the age range was 43 to 93 years with a median of 72 years.

Forty-eight black patients without glaucoma were randomly selected from the ophthalmology clinic patient population for HLA typing. These patients had a variety of nonglaucomatous ophthalmic conditions, and the majority were cataract or refractive patients. The male:female ratio of this group was 12:36; the age range was 41 to 93 years with a median age of 68 years.

Fifty-one black, normal, healthy persons previously HLA-phenotyped were used as controls. This control group of blacks was characterized by serum reactions with anti-HLA antisera from the Sixth and Seventh International Histocompatibility Testing Workshops, the First and Second HLA Workshops of the Americas, and with local and National Institutes of Health antisera. The male:female ratio in this population was 4:47 and the age range was 25 to 40 years. These persons were unrelated laboratory or hospital personnel.

Published data[10] on HLA antigen frequencies for North American blacks from the Sixth International Workshop, com-

prising 356 randomly selected nonrelated individuals, were used for nonstatistical comparison.

HLA typing—HLA typing was performed by a modification of Amos' two-stage lymphocytotoxicity technique.[11,12] A 10-ml sample of heparinized whole blood from each eye patient was obtained by eye clinic personnel. The samples were not disease-identified on submission to the tissue typing laboratory. A relatively pure suspension of lymphocytes was prepared by red blood cell sedimentation with methyl-cellulose, followed by granulocyte elimination with iron filings, and subsequent elimination of contaminating red blood cells with specific anti-A, anti-B, or anti-H. Lymphocytes were resuspended in Hanks' solution at a concentration of 2×10^6/ml. A panel of 250 HLA-antisera was used for typing. These antisera, comprised of local and National Institutes of Health antisera, represented 16 A-locus antigens and 19 B-locus antigens. Those lymphocytes exhibiting HLA-B7, HLA-Bw22, or HLA-Bw42 activity were reacted with 40 additional antisera corresponding to these antigens. These additional antisera were used in the Sixth and Seventh International HLA Workshops to identify these specificities.

The lymphocytotoxicity procedures were performed in plastic microtiter trays by incubating approximately 2,000 lymphocytes with 0.001 ml of each antiserum 30 minutes, a subsequent wash with Barbitol buffer, a further 60-minute incubation with 0.005 ml of rabbit complement, and then the addition of trypan blue to demonstrate cytotoxicity. The percent cytotoxicity for each antiserum was evaluated and the presence or absence of each HLA antigen was recorded, resulting in the HLA phenotype for each person. The 96 individuals thus phenotyped were then assigned to the POAG or non-POAG group.

The incidence of each of the 16 A-locus antigens and 19 B-locus antigens was tabulated for the POAG patients, the non-POAG patients, and the control group. The percent antigen frequency was calculated for each antigen in each group.

Statistical analysis—Contingency 2×2 tables were constructed for those antigens that demonstrated an apparent suggestive difference in incidence in the POAG vs non-POAG groups. From these 2×2 tables, chi-square values were calculated by using Yates' correction for continuity.[13]

Individual P values were calculated from the chi-square values. No statistical evaluation was made between the POAG patients and the local panel group because the variables (sex, age, typings done on different sera at different times, and the like) could not be controlled adequately for meaningful evaluation of all antigens.

RESULTS

Table 1 demonstrates the incidence of the 16 A-locus antigens and the 19 B-locus antigens in the black POAG patients and the non-POAG patients HLA phenotyped for this study. Table 1 also includes the frequency for the same antigens for our control group of blacks who had been typed on many additional sera not available to the patient populations. Table 1 lists in parentheses the HLA antigen frequencies in percent for the three black populations and the frequencies from accumulated data on 356 North American blacks typed with the Sixth International HLA Workshop sera.[10] We noted several disparities for antigen incidence (namely, a two-, three-, five-, or sixfold increase or decrease) between these two ophthalmic populations; 2×2 tables, chi-square values, and P values for these ten HLA antigens (HLA-A2, HLA-A3, HLA-Aw34, HLA-A29, HLA-Aw33, HLA-Aw36, HLA-B7, HLA-B14, HLA-Bw22, and HLA-Bw42) were calculated. Table 2 lists the chi-square values and the

TABLE 1

INCIDENCE OF HLA ANTIGENS IN 48 POAG PATIENTS
48 NON-POAG PATIENTS, AND 51 CONTROL GROUP PERSONS

HLA Antigen	POAG No. (%)	Non-POAG No. (%)	Control Group No. (%)	North American Black Population (356)[10] (%)
A1	6 (13)	6 (13)	3 (6)	12
A2	10 (21)	20 (42)	14 (27)	31
A28	8 (17)	10 (21)	7 (14)	18
A3	12 (26)	7 (15)	11 (22)	14
Aw23	10 (21)	7 (15)	16 (31)	21
Aw24	4 (8)	5 (10)	1 (2)	9
A25	0	0	0	2
A26	2 (4)	2 (4)	3 (6)	7
Aw34	6 (13)	2 (4)	6 (12)	6
A11	1 (2)	1 (2)	0	3
A29	6 (13)	2 (4)	3 (6)	5
Aw30	13 (27)	13 (27)	14 (27)	22
Aw31	0	1 (2)	3 (6)	11
Aw32	1 (2)	0	2 (4)	4
Aw33	6 (13)	1 (2)	8 (16)	12
Aw36	2 (4)	5 (10)	1 (2)	1
1-A-Ag*	9 (19)	14 (29)	10 (20)	19
B5	4 (8)	5 (10)	16 (31)	9
B7	14 (29)	6 (13)	8 (16)	22
B8	0	4 (8)	2 (4)	6
B12	8 (17)	5 (10)	5 (10)	15
B13	1 (2)	1 (2)	0	2
B14	2 (4)	6 (13)	3 (6)	5
B15	7 (15)	9 (19)	4 (8)	4
Bw16	2 (4)	1 (2)	2 (4)	3
B17	12 (26)	13 (27)	17 (33)	24
B18	2 (4)	5 (10)	3 (6)	5
Bw21	1 (2)	5 (10)	7 (14)	10
Bw22	3 (6)	0	4 (8)	3
B27	0	2 (4)	2 (4)	2
Bw35	17 (35)	13 (27)	3 (6)	36
B37	0	0	1 (2)	1
B40	3 (6)	1 (2)	3 (6)	4
Bw41	0	1 (2)	1 (2)	1
Bw42	9 (19)	4 (8)	7 (14)	11
Bw45	4 (8)	7 (15)	4 (8)	8
1-B-Ag†	7 (15)	8 (17)	10 (20)	34

*1-A-Ag indicates number of persons typing for only one A antigen.
†1-B-Ag indicates number of persons typing for only one B antigen.

P values for the ten statistically evaluated HLA antigens. None of the antigens in question revealed a statistically significant difference between the POAG and non-POAG populations by using the criteria of the HLA and Disease Registry.

Any patient reacting with anti-B7, anti-Bw22, or anti-Bw42 antisera was also examined with the Sixth and Seventh International Workshop antisera to further clarify the HLA splits of anti-Bw22 and anti-Bw42. This provided a means for statistical analysis of these three antigens between the POAG, non-POAG, and control group populations. Using the same statistical methods, we found no significant difference (Table 3).

Of the 96 samples submitted from the

TABLE 2

CHI SQUARE AND P VALUES FOR HLA ANTIGENS WITH VARYING INCIDENCES BETWEEN POAG AND NON-POAG PATIENTS

HLA Antigen	Chi-square Value	P Value
A2	3.9273	.0475
A3	1.0499	.3055
Aw34	1.2273	.2679
A29	1.2273	.2679
Aw33	2.4655	.1164
Aw36	.6164	.5676
B7	3.0947	.0785
B14	1.2273	.2679
Bw21	1.6000	.2059
Bw42	1.424	.2328

Eye Clinic, three POAG and three non-POAG samples were typed blank for both an A antigen and a B antigen, suggesting the possibility of homozygosity for the HLA region. Five of these six patients had the HLA-Bw35 antigen (Table 4).

DISCUSSION

We could not confirm in this study the increases in HLA-B7 and HLA-B12 or the decreases in HLA-A1 and HLA-A11 in black glaucoma patients reported by Shin[6] and Becker.[8] No statistically significant increase or decrease in these POAG patients was found for any HLA antigen when the HLA and Disease Registry criteria were used; namely, statistical significance is obtained when the P value is 10^{-4} or less.[1] The highest P value in this study is for HLA-A2 (P=.0475) and is significant at the 5% level. It has been suggested that the P value for any significant association be multiplied by the number of comparisons made (antigens typed in this case) to reach a "real significance level."[14] With those mathematical manipulations, the P value for HLA-A2 becomes 1.6625 and nonsignificant.

In the past, many antisera used to define HLA-B7 have also contained anti-Bw22 and anti-Bw42. Only within the past five years have the latter two antigens been split from the HLA-B7. Perhaps the difference between our data and Shin's and Becker's data is a secondary function of our definitions of HLA-Bw22 and HLA-Bw42, which would decrease the frequency of a broad HLA-B7. For instance, if we pool our B7-Bw22-Bw42 data, we get an incidence of 25 vs ten for the POAG vs non-POAG populations, a chi-square value of 8.813, and a P value of .003.

The pooled data from the Sixth International Workshop on the frequency of HLA antigens in 356 North American blacks is listed (Table 1), and the percent frequency of each antigen between those individuals and our POAG patients hardly differs. Minor differences are expected when one considers that new antigens and splits of antigens have occurred in the intervening four years. Some antigens (namely, HLA-Aw36 and HLA-Bw42) are now more easily identified. These changes are partially reflected in the decrease in the number of persons who typed for only one B-locus antigen then (23%) as opposed to now (15%).

No clinical or biological significance is attached to the data that 6% of the patients in this study typed blank for both an A and a B antigen, suggesting homozy-

TABLE 3

PATIENTS OR PANEL MEMBERS POSITIVE FOR HLA ANTIGENS OF THE SEVEN GROUP

Subjects (No.)	HLA -B7	HLA -Bw22	HLA -Bw42	Total Subjects
POAG patients (48)	14*	3	9	22
Non-POAG patients (48)	6		4	10
Control group (51)	8†	5	6	15

*Three persons also had the HLA-Bw22 antigen; one, the HLA-Bw42 antigen.

†Two persons also had the HLA-Bw22 antigen; two, the HLA-Bw42 antigen.

TABLE 4

A AND B LOCUS HLA ANTIGENS IN POAG AND NON-POAG PATIENTS

Patient No.	A Locus HLA Antigens	B Locus HLA Antigens	Disease
26	Aw36,X*	Bw35,X	Non-POAG
38	Aw33,X	Bw35,X	POAG
44	Aw34,X	Bw35,X	POAG
49	Aw30,X	Bw42,X	POAG
102	A 28,X	Bw35,X	Non-POAG
103	A 3,X	Bw35,X	Non-POAG

*X represents homozygosity of the antigen for that locus or the presence of an antigen that is not definable by the sera used.

gosity for the HLA region, is not clinically or biologically significant. We do not frequently encounter this phenomenon in our local routine typing, however. It is interesting that five of these patients have the Bw35 antigen since Aviner and associates[4] reported an increase in HLA-Bw35 in POAG. Whether these patients are truly HLA homozygous is being investigated.

SUMMARY

We compared the HLA antigen frequencies in black primary open-angle glaucoma patients to those in black nonglaucomatous patients; normal, nondiseased black persons; and nondiseased North American blacks. We found no statistically significant alteration in HLA antigen frequencies in black open-angle glaucoma patients as compared to a control population.

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THE LONG-TERM EFFECTS OF IRIDECTOMY FOR PRIMARY ACUTE ANGLE-CLOSURE GLAUCOMA

THEODORE KRUPIN, M.D., KENNETH B. MITCHELL, M.D., MARK F. JOHNSON, M.D., AND BERNARD BECKER, M.D.

St. Louis, Missouri

The management of primary acute angle-closure glaucoma requires surgery. Iridectomy is most frequently performed both in the acutely involved eye and the asymptomatic narrow-angle fellow eye. However, some reports suggest that late persistent intraocular pressure increase and visual field loss may occur in both the glaucomatous and fellow eyes after iridectomy.[1] Therefore, primary filtering surgery is sometimes advised instead of simple iridectomy.[2,3] Other investigators indict iridectomy as a cause of cataract.[4,5] We performed a retrospective clinical study of patients treated with iridectomy for primary acute angle-closure glaucoma to determine the incidence of postoperative intraocular pressure increase and decreased visual acuity.

SUBJECTS AND METHODS

The study included 45 patients who had primary acute angle-closure glaucoma between 1969 and 1974. Forty-three patients (93%) were women. The average age at the time of the acute attack was 64.5 ± 8.9 years (± SEM). The diagnosis was suggested by the presence of pain and blurred or halo vision, and was confirmed by the presence of increased intraocular pressure and closed iridocorneal angle. Unilateral primary acute angle-closure occurred in 41 patients (22 left eyes) who demonstrated a narrow anterior chamber angle in the asymptomatic, normotensive fellow eye. Three patients developed acute angle closure in the second eye while in the hospital, and one patient had a bilateral acute attack.

Forty-four patients had bilateral iridectomies (33 peripheral, 11 sector), whereas one patient was treated with iridectomy in the angle-closure eye and with topical pilocarpine in the contralateral eye. Therefore, 49 eyes had an iridectomy for primary acute angle-closure glaucoma (41 unilateral, four bilateral), and 40 eyes had a prophylactic iridectomy in an asymptomatic fellow eye. The duration of postoperative follow-up was 52.3 ± 3.6 months.

RESULTS

Glaucoma control—EYES WITH ACUTE ANGLE CLOSURE—Previous signs or symptoms of angle closure had been present in 17 (35%) of the 49 eyes before the acute attack and subsequent iridectomy. The duration of symptoms of the acute attack before the patient came for therapy ranged from four hours to two weeks. Medical therapy ended the attack before surgery in 45 (92%) of the eyes. In four eyes, medical treatment was unsuccessful (failure to decrease the intraocular pressure or open the closed angle), and surgery was performed on these eyes with increased intraocular pressure.

Thirty-seven (76%) of the eyes with acute attacks have maintained postoperative intraocular pressures of 21 mm Hg or less (mean ± SEM, 16.6 ± 0.5 mm Hg) with no medical therapy. These eyes have had normal visual fields for the duration

From the Department of Ophthalmology and the Oscar Johnson Institute, Washington University School of Medicine, St. Louis, Missouri. This study was supported in part by research grant EY 00336 and by Research Career Development Award EY 00082 (Dr. Krupin) from the National Eye Institute, Bethesda, Maryland. Drs. Mitchell (1977-1978) and Johnson (1976-1977) were Heed Foundation Fellows.

Reprint requests to Theodore Krupin, M.D., Department of Ophthalmology, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110.

of the study. Twelve (24%) of the eyes that had acute attacks developed intraocular pressures over 21 mm Hg (range, 22 to 40 mm Hg) 0.5 to 72 months (mean, 12.2 months) following iridectomy. Two of these 12 eyes had peripheral anterior synechiae with sealed iridocorneal angles. The intraocular pressure was controlled medically in one eye, whereas the other eye required filtration surgery seven years after iridectomy for progressive disk cupping. The irodocorneal angle was deeper following iridectomy in the other ten eyes with the increased intraocular pressure presumably secondary to trabecular dysfunction associated with the acute attack. Eleven of these eyes were treated with either pilocarpine or epinephrine which decreased intraocular pressure from a mean of 28.0 ± 1.9 to 18.7 ± 1.0 mm Hg. Two of the medically treated eyes demonstrated nonprogressive glaucomatous field defects after iridectomy, whereas the remainder have continued to have normal visual fields. Thus, 48 (98%) of 49 eyes with acute angle-closure glaucoma were controlled, with or without medical therapy, after iridectomy.

ASYMPTOMATIC, NORMOTENSIVE FELLOW EYES—Thirty-five (88%) of the 40 eyes treated with prophylactic iridectomy had untreated postoperative intraocular pressure of 21 mm Hg or less. Five (12%) of the prophylactically operated eyes developed intraocular pressures greater than 21 mm Hg (range, 22 to 25 mm Hg) 14 to 72 months (mean, 33.8 ± 11.4 months) following their iridectomy. These five eyes were treated with either topical epinephrine or pilocarpine, which decreased intraocular pressure from a mean of 22.8 ± 1.0 to 17.8 ± 1.7 mm Hg. No glaucomatous field defects have developed in any of the fellow eyes treated with prophylactic iridectomy.

Postoperative visual acuity—EYES WITH ACUTE ANGLE CLOSURE—Visual acuity was unchanged in 22 (45%) eyes following iridectomy. The visual loss in the remaining eyes (Table) was thought to be consistent with lenticular changes. Of the 11 (22%) eyes with a decrease in visual acuity greater than six lines, five underwent successful cataract surgery, whereas the remainder were not treated.

ASYMPTOMATIC NORMOTENSIVE FELLOW EYES—Visual acuity was unchanged following prophylactic peripheral iridectomy in 25 (63%) fellow eyes, and decreased by one to six lines in 14 (35%) eyes (Table). Cataract surgery was performed on the only eye with visual acuity loss greater than six lines.

DISCUSSION

Primary acute angle-closure glaucoma is a bilateral disease. Approximately 78% of patients with primary acute angle-closure glaucoma develop an acute attack in the initially asymptomatic normotensive fellow eye if this eye is not treated.[6] Of the fellow eyes treated prophylactically with miotics, 39 to 54% develop an acute attack.[6,7] In one series of 190 patients with unilateral, primary acute angle-closure glaucoma, acute attacks occurred in 54% of 106 fellow eyes treated medically, but in none of the 84 eyes treated with prophylactic peripheral iridectomy. Therefore, both eyes require surgical therapy.

Recently questions have arisen as to

TABLE

CHANGE IN VISUAL ACUITY FOLLOWING IRIDECTOMY

Postoperative Decrease (Snellen Lines)	Eye Condition	
	Acute Angle Closure	Prophylactic Treatment
No change	22 (45%)	25 (63%)
1 - 2 lines	8 (16%)	9 (23%)
3 - 4 lines	5 (11%)	4 (10%)
5 - 6 lines	3 (6%)	1 (2%)
> 6 lines	11 (22%)	1 (2%)

which procedure is best for this disease. In our opinion, iridectomy is the preferred procedure in primary acute angle-closure glaucoma. The effectiveness of iridectomy depends on several factors. These include the presence of pupillary block as a cause of angle closure and the extent of trabecular dysfunction associated with angle closure itself or resultant synechiae. Various preoperative findings may have a predictive value in determining whether simple iridectomy alone will result in a permanent cure. These include the duration of the acute attack,[8] gonioscopy (pre- and intraoperative),[9–11] ophthalmoscopy, and visual field examination. None of these is totally reliable in predicting which patients may need more than an iridectomy for permanent pressure control. Also, iridectomy is a simpler and safer procedure than filtering surgery even when the acute attack is present for longer than 48 hours, when the angle appears sealed, and when both intraocular pressure and outflow facility are abnormal during treatment with miotics and carbonic anhydrase inhibitors.[12,13]

The present study confirms the efficacy and safety of iridectomy for primary acute angle-closure glaucoma. Other studies often fail to separate cases in which iridectomy is performed for acute, chronic, or combined mechanism glaucoma. Females predominate (93%) in our series as in others.[4] Seventy-six percent of the eyes with primary acute angle closure in this study maintained normal intraocular pressures and visual fields without therapy after iridectomy. These results are similar to those reported by Murphy and Spaeth[14] (61%), Floman, Berson, and Landau[4] (70%), and Hyams, Keroub, and Pokotilo[15] (74%). Whereas postiridectomy increases of intraocular pressure were recorded in 12 eyes (24%) of the acute angle-closure group in this series, only one eye of these 12 was not controlled with medical therapy. Of the 40 fellow eyes in our study, 12% showed mild increases of intraocular pressure, whereas 88% remained normotensive and none demonstrated visual field loss or required filtering surgery. Iridectomy allows the use of strong miotics or epinephrine if treatment for persistent pressure increase becomes necessary. Should medical control not be achieved following iridectomy, subsequent filtration surgery may be performed easily, and the success of this surgery is not adversely affected by the previous iridectomy.[12]

Iridectomy is supposedly associated with an increased incidence of cataract after angle-closure glaucoma.[4,5] Sugar[16] reported cataracts (visual acuity <6/18 [20/60]) in approximately 30% of patients two to 17 years after bilateral iridectomy. Murphy and Spaeth[14] found a decrease in visual acuity of one to three lines in 12 of 33 eyes with acute angle closure, and in five of 21 prophylactically treated eyes after iridectomy.[14] The development of cataract after iridectomy appears to be directly related to the patient's age and the injuries incurred during the acute attack and the surgical intervention. Our findings of an incidence of visual acuity loss higher in the acute eye than in the prophylactically treated eye are similar to those of Godel and Regenbogen.[5]

SUMMARY

Forty-nine eyes were treated with iridectomy for primary acute angle-closure glaucoma. Forty asymptomatic, normotensive fellow eyes were similarly treated. The duration of follow-up after surgery was 52.3 ± 3.6 months. Thirty-seven (76%) of the eyes with acute attacks were cured by iridectomy alone and required no medical therapy. Twelve eyes (24%) developed increased intraocular pressure following iridectomy, but only one eye

(2%) required filtering surgery. Eighty-eight percent of the asymptomatic, normotensive fellow eyes required no subsequent therapy, and none developed visual field defects. Visual acuity was unchanged in 22 of 49 (45%) of the acutely involved eyes and decreased more than six lines in 11 (22%) eyes. In the 40 fellow eyes, visual acuity was unchanged in 63% and decreased more than six lines in only one (2%) eye.

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PROGNOSTIC FACTORS OF INTRAOCULAR PRESSURE AFTER APHAKIC KERATOPLASTY

RANDALL J. OLSON, M.D. AND HERBERT E. KAUFMAN, M.D.
New Orleans, Louisiana

In 1969 Irvine and Kaufman[1] showed that high intraocular pressure commonly occurred after aphakic keratoplasty and keratoplasty combined with lens extraction. Many patients with an extreme postoperative pressure increase seemed to have a persistent increase of the intraocular pressure indefinitely even though they had no indication of glaucoma before the surgery. We did a retrospective study of the pressure course of 68 consecutive patients (81 eyes) who underwent aphakic keratoplasty and keratoplasty combined with lens extraction to determine the frequency of persistently increased intraocular pressure after such keratoplasty.

SUBJECTS AND METHODS

We reviewed the charts of all patients at the University of Florida who had undergone aphakic keratoplasty or keratoplasty combined with lens extraction from July 1, 1975, through April 16, 1976. Eight patients who had wound leaks or active infectious keratitis at the time of surgery were excluded from the study.

All pressures had been measured by Mackay-Marg electronic applanation tonometry because our earlier findings[2] indicated it to be an accurate method in determining intraocular pressure in the presence of corneal disease and keratoplasty.

At any time during the postoperative course, all patients with intraocular pressures greater than 25 mm Hg began receiving glaucoma medication because optic nerve head and visual field follow-up was difficult in these patients who were only irregularly seen by us. Treatment consisted of carbonic anhydrase inhibitors, and miotics were added when this was ineffective. When the eye was quiet, cycloplegics were stopped. Cyclocryotherapy had been used if the intraocular pressure stayed consistently above 30 mm Hg despite medical management.

RESULTS

Vitrectomies were required in 41 (87.2%) of the aphakic keratoplasties and 12 (35.3%) of the keratoplasties combined with lens extraction. The pressure course did not significantly differ between those patients who had vitrectomies and those who did not. Alphachymotrypsin was not used for any of the lens extractions. All but eight of the 81 patients had a 7.5-mm keratoplasty, with six requiring an 8.0-mm keratoplasty, and two, a 7.0-mm keratoplasty. Five of the 81 patients, distributed among all four groups, had donor corneal buttons larger than the recipient holes.

We analyzed the data according to whether or not the eye had evident high pressure (>25 mm Hg) or was receiving glaucoma treatment preoperatively, and looked separately at those who were already aphakic before keratoplasty and those who underwent lens extraction with keratoplasty. The patients who had preoperative high pressure or were taking glaucoma medication and underwent a combined procedure were significantly younger than those of the other three groups ($P<.05$).

The aphakic group who had preopera-

From the Department of Ophthalmology, Louisiana State University School of Medicine, New Orleans, Louisiana. This study was supported in part by Grant EY00266 from the National Eye Institute and a Bausch and Lomb fellowship (Dr. Olson).

Reprint requests to Randall J. Olson, M.D., Louisiana State University Eye Center, 136 S. Roman St., New Orleans, LA 70112.

tive high-pressure or who were receiving glaucoma medication had a higher maximum postoperative pressure than those without evidence of preoperative glaucoma during the one- to six-month postoperative period (P=.017) (Table 1 and Figure). The maximum postoperative pressure in the one- to six-month period for both preoperative high pressure groups was higher than that of those who had no evidence of glaucoma preoperatively (P=.0015). There were no other significant differences, and we found those who were included in the high preoperative pressure group because of the medication they were taking but who had intraocular pressures less than 25 mm Hg had a postoperative pressure course similar to that of those with intraocular pressure higher than 25 mm Hg, many of whom were also receiving glaucoma medication (Table 2).

We also examined our results in terms

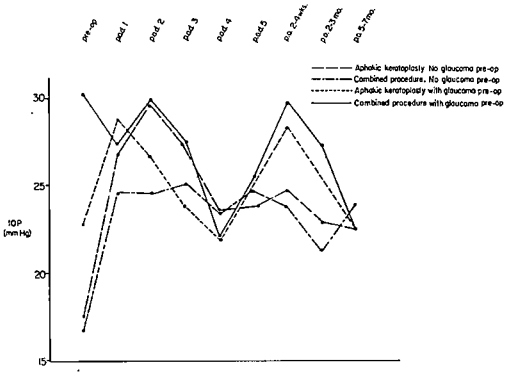


Figure (Olson and Kaufman). Intraocular pressure course after keratoplasty.

of whether or not patients had high intraocular pressures during the first postoperative week. Among the 37 patients with intraocular pressures greater than 35 mm Hg during the first postoperative week, 36 (97%) of those patients were receiving glaucoma medication at discharge from the hospital, and 28 (76%) required glaucoma medication for pressure control at

TABLE 1

INTRAOCULAR PRESSURES (mm Hg) BEFORE AND AFTER KERATOPLASTY IN APHAKIA OR COMBINED KERATOPLASTY AND CATARACT EXTRACTION

	Without Preoperative Glaucoma		With Preoperative Glaucoma	
	Aphakic	Combined	Aphakic	Combined
No. of eyes	21	23	26	11
Mean age	67.9	69.3*	65.2	59.4*
Preoperative IOP	17.4†	16.5‡	22.7†	30.2‡
Postoperative IOP				
Day 1	26.6	24.6	28.8	27.3
Day 2	29.6	24.5	26.6	29.9
Day 3	27.1	25.1	23.7	27.5
Day 4	23.5	23.3	21.8	22.0
Day 5	23.7	24.7	25.2	25.3
Mean IOP, Days 1-5	26.2	24.4	25.2	26.4
Maximum IOP, Days 1-5	32.1	30.6	34.8	34.0
IOP, 2-4 wks	24.8	23.7	28.3	29.8
IOP, 2-3 mos	22.9	21.1	25.4	27.3
IOP, 5-7 mos	22.4	23.9	22.5	22.4
Mean IOP, 2 wks -7 mos	23.3	22.8	25.4	26.4
Maximum IOP, 2 wks -7 mos	30.5§	29.0	38.3§	33.7

*P = .031.
†P = .002.
‡P = .00004.
§P = .017.

TABLE 2

OUTCOME AFTER KERATOPLASTY IN APHAKIA OR COMBINED WITH CATARACT EXTRACTION IN PATIENTS WITH MAXIMUM PRESSURE MORE THAN 35 mm Hg DURING FIRST POSTOPERATIVE WEEK

	Without Preoperative Glaucoma		With Preoperative Glaucoma	
	Aphakic (N=10)	Combined (N=8)	Aphakic (N=15)	Combined (N=4)
Glaucoma medication needed				
At discharge from hospital (%)	10 (100)	8 (100)	14 (93)	4 (100)
Six months postoperatively (%)	7 (70)	6 (75)	11 (73)	4 (100)
Cyclocryotherapy (%)	2 (20)	1 (12)	3 (20)	1 (25)
Maximum IOP>35 mm Hg during late postoperative period* (%)	6 (60)	2 (25)	7 (47)	3 (75)
Vitrectomies (%)	8 (80)	6 (75)	14 (93)	2 (50)

*Two weeks to seven months postoperatively.

six months. During the one- to six-month postoperative period, 18 (49%) of those patients had at least one pressure greater than 35 mm Hg, and seven (19%) required cyclocryotherapy for pressure control. There was no evident difference between those with and those without preoperative high pressure (Table 3).

Among the 44 patients who did not have postoperative pressures higher than 35 mm Hg, there was a similarly high number needing medical or cryosurgical control of pressure if there had been preoperative increased pressure (Table 4). However, in the 26 patients with no evidence of preoperative glaucoma, a significant number had problems with increased pressure chronically. We decided to subdivide this latter group further, separating those patients with pressures between 28 and 35 mm Hg during the first postoperative week from those whose pressures were never higher than 27 mm Hg. Of the 11 patients with pressures between 28 and 35 mm Hg, eight (73%) were receiving glaucoma therapy at dis-

TABLE 3

OUTCOME AFTER KERATOPLASTY IN APHAKIA OR COMBINED WITH CATARACT EXTRACTION IN PATIENTS WITH MAXIMUM PRESSURE LESS THAN 35 mm Hg DURING FIRST POSTOPERATIVE WEEK

	Without Preoperative Glaucoma		With Preoperative Glaucoma	
	Aphakic (N=11)	Combined (N=15)	Aphakic (N=11)	Combined (N=7)
Glaucoma medication needed:				
At discharge from hospital (%)	3 (27)	7 (47)	5 (46)	4 (57)
Six months postoperatively (%)	3 (27)	7 (47)	8 (73)	5 (71)
Cyclocryotherapy (%)	2 (18)*	0 (0)	4 (36)	1 (14)
Maximum IOP>35 mm Hg during late postoperative period† (%)	3 (27)	3 (20)	9 (82)	4 (57)
Vitrectomies (%)	9 (82)	6 (40)	10 (91)	3 (43)

*Extensive peripheral anterior synechiae in one patient.
†Two weeks to seven months postoperatively.

TABLE 4

INTRAOCULAR PRESSURE COURSE AFTER KERATOPLASTY IN APHAKIA OR COMBINED WITH CATARACT EXTRACTION IN PATIENTS WITH GLAUCOMA PREOPERATIVELY

	Preoperative Intraocular Pressure	
	25 mm Hg (N=19) with or without Glaucoma Medication	25 mm Hg (N=18) with Glaucoma Medication
Preoperative IOP	30.6	18.9
Postoperative IOP		
Day 1	26.9	29.9
Day 2	25.3	30.1
Day 3	23.5	26.2
Day 4	21.6	22.2
Day 5	25.0	25.5
Maximum IOP, Days 1-5	31.2	38.2
IOP, 2-4 wks	30.2	27.8
IOP, 2-3 mos	25.6	26.2
IOP, 5-7 mos	22.8	23.9
Maximum IOP, 2 wks -7 mos	35.7	36.7

charge from the hospital, and six (55%), at six months. One (9%) required cyclocryotherapy. Those results were similar to those in patients who had intraocular pressure higher than 35 mm Hg in the first postoperative week. The results were also similar to those in 18 patients with preoperative high pressure and only moderate pressure increase less than 35 mm Hg during the first postoperative week. Only nine (50%) of these 18 patients were discharged from the hospital while receiving glaucoma medication, but 13 (72%) had at least one postoperative pressure greater than 35 mm Hg in the late postoperative period and 13 (72%) were receiving glaucoma medication at six months. Five of those patients (28%) required cyclocryotherapy for pressure control. We found no significant correlation between the preoperative and postoperative intraocular pressures in this group.

Predictably, those patients without evidence of preoperative glaucoma and no pressures higher than 27 mm Hg during the first postoperative week had benign late postoperative pressures. None of them was discharged while receiving glaucoma medication therapy. Three of the 15 required postoperative glaucoma medication at six months. One of those three had extensive peripheral anterior synechiae and severe pressure problems requiring cyclocryotherapy; the pressure increase of the other two was mild.

Nineteen cyclocryotherapies were performed on 14 patients when medical control of the pressure proved impossible. The mean intraocular pressure just before this treatment was 46.9 mm Hg (range, 38 to 65 mm Hg). Five patients were treated within the first two months, and of these five, four needed additional treatment at three months after surgery in three cases and at five weeks after surgery in one case. The fifth patient had preoperative glaucoma, and all pressures were above 40 mm Hg during the first two postoperative weeks. Cyclocryotherapy was performed successfully at two weeks (intraocular pressure, (50 mm Hg) with good pressure control afterwards.

Fifty-five patients were discharged from the hospital while receiving glaucoma medication, and 40 of them were still taking medication six months after surgery. Although they were taking glaucoma medication, all but three of these 40 patients had intraocular pressures greater than 30 mm Hg (mean, 36.9 mm Hg for all 40 patients) during the one- to seven-month postoperative period. Eleven patients with a mean intraocular pressure of 37.1 mm Hg (range 28 to 50 mm Hg) began glaucoma medication after discharge from the hospital.

Discussion

This study verifies our impression that increased intraocular pressure in aphakic keratoplasty is common and may be a persistent problem even in patients without preoperative glaucoma.

In 1972, Wood, West, and Kaufman[3] showed that in those patients with increased intraocular pressure in the acute postoperative period, the general trend was toward decreased intraocular pressure with no significant difference in those with or without preoperative glaucoma. This does not conflict with our present results because their study included only patients who already had increased pressure during the first postoperative week. The present study suggests that the only group without a high incidence of persistently increased pressure is that which had no preoperative glaucoma and also did not have a pressure of higher than 27 mm Hg in the first postoperative week.

The postoperative pressure courses were similar whether glaucoma was suspected preoperatively or not. The postoperative pressure courses (Figure) had a remarkably similar bipeaked character, with the highest pressure in the early postoperative period and at the two- to four-week postoperative period. The times for the lowest pressures were at the fourth postoperative day and the five- to seven-month period. Examination of the pressure on the first or second postoperative visit is therefore important because the high pressure is likely to return even if the intraocular pressure has not increased at the end of the first week. The only significant difference in the graphic postoperative pressure course between those with and those without suspected preoperative glaucoma is that patients who had suspected preoperative glaucoma have higher maximum pressures in the late postoperative period.

Rather than treat the pressure increase medically, which can be difficult,[3,4] or with cryotherapy,[3,5] we believe it possible to prevent a postoperative pressure increase by using a donor button larger than the recipient hole.[6–9] The present study shows the persistence of increased intraocular pressure when it occurs after aphakic keratoplasty and, therefore, the importance of such preventative measures.

Summary

In 68 consecutive patients who had undergone aphakic keratoplasty and keratoplasty combined with cataract extraction, patients with pressure problems during the first postoperative week were likely to have chronic pressure problems whether glaucoma was suspected preoperatively or not. Furthermore, those with preoperative glaucoma, even though pressures during the first week were relatively normal, were likely to have reoccurrence of their glaucoma. The preoperative pressures did not indicate which patients would develop persistently increased postoperative pressures. The only patients spared pressure problems were those who had no evidence of glaucoma preoperatively and who also had normal intraocular pressure during the first postoperative week.

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Ophthalmic miniature

"We all want a little patching and repairing from time to time," he chirped. "Like a ship, my dear sir,—exactly like a ship. Sometimes the hull is out of order, and we consult the surgeon; sometimes the rigging, and then I advise; sometimes the engines, and we go to the brain-specialist; sometimes the look-out on the bridge is tired, and then we see an oculist. I should recommend you to see an oculist. A little patching and repairing from time to time is all we want. An oculist, by all means."

Dick sought an oculist,—the best in London. He was certain that the local practitioner did not know anything about his trade, and more certain that Maisie would laugh at him if he were forced to wear spectacles.

"I've neglected the warnings of my lord the stomach too long. Hence these spots before the eyes, Binkie. I can see as well as I ever could."

Rudyard Kipling, *The Light That Failed*

TOXICITY OF COMBINED THERAPY WITH CARBONIC ANHYDRASE INHIBITORS AND ASPIRIN

CHARLES J. ANDERSON, M.D., PAUL L. KAUFMAN, M.D., AND RODNEY J. STURM, M.D.

Madison, Wisconsin

Systemic acidosis caused by renal bicarbonate loss[1,2] and perhaps erythrocyte CO_2 retention[3] is an inevitable concomitant of carbonic anhydrase inhibitor therapy. Although the acidosis is rarely severe, it may cause the symptom complex of malaise, fatigue, weight loss, depression, anorexia, and loss of libido which frequently occurs in patients receiving chronic carbonic anhydrase inhibitor therapy, and often requires the discontinuance of such therapy.[4]

Salicylates in high doses can cause severe acid-base imbalance, central nervous system dysfunction, and death.[1,5-7] Toxicity seems related to tissue rather than blood salicylate levels.[1,5,8] Nonionized salicylic acid passes from the bloodstream into the central nervous system and other cells much more rapidly than does ionized salicylate.[5,8] Systemic acidosis, which increases the proportion of nonionized drug, therefore enhances penetration into the central nervous system and other tissues.[1,3,5,8]

Thus, the acidosis caused by carbonic anhydrase inhibitors may increase the likelihood and severity of salicylate toxicity in patients taking salicylates, and conversely, the acidosis caused by salicylates may increase the likelihood and severity of the acidotic symptom complex[4] in patients taking carbonic anhydrase inhibitors. We describe herein two patients in whom the combination of carbonic anhydrase inhibitor therapy of glaucoma and aspirin therapy of chronic arthritis was almost disastrous.

From the Department of Ophthalmology, University of Wisconsin Medical School, Madison, Wisconsin.

Reprint requests to Charles J. Anderson, M.D., Department of Ophthalmology, University of Wisconsin Hospitals, 1300 University Ave., Madison, WI 53706.

CASE REPORTS

Case 1—a 67-year-old woman with longstanding rheumatoid arthritis underwent elective cataract surgery on Dec. 15, 1976. The following day, she began receiving 500 mg of acetazolamide twice a day. At discharge three days later, the dosage was changed to 250-mg acetazolamide tablets four times a day. She continued to take her preadmission aspirin dosage of 975 to 1,600 mg five times daily, which she had been taking uneventfully for 18 years. On Jan. 6, 1977, she was brought to the emergency room somnolent and complaining of a three-week history of progressively worsening anorexia, lethargy, decreased motivation, insomnia, tinnitus, and tachypnea. Respirations were 24 per minute, deep and regular. Serum chemistry studies showed the following: sodium, 145 mEq/liter; potassium, 3.5 mEq/liter; chloride, 121 mEq/liter; nonfasting glucose, 137 mg/100 ml; and blood urea nitrogen, 37 mg/100 ml. Venous blood gases were: pCO_2, 18 mm Hg; CO_2, 10 mEq/liter; and pH, 7.32. The salicylate level was 24 mg/100 ml and serum acetone was nondetectable. On Jan. 7, 1977, arterial blood gases revealed: $p0_2$, 100 mm Hg; pCO_2, 22 mm Hg; pH, 7.39; base excess, 10.1 mEq/liter; buffered base, 36.5 mEq/liter; standard bicarbonate, 16.4 mEq/liter; actual bicarbonate, 12.9 mEq/liter; and total CO_2, 13.5 mEq/liter. Other studies included arterial lactate, 0.6 mEq/liter (normal < 2.0 mEq/liter); serum creatinine, 1.2 mg/100 ml; and urine pH, 6.0. Complete blood cell count and chest x-ray films were normal. Treatment consisted of discontinuation of aspirin and acetazolamide therapy, and intravenous administration of fluids, bicarbonate, and potassium. Dramatic improvement of symptoms and electrolytes resulted. She has remained well while taking 125 mg of acetazolamide twice a day and 3.25 g of aspirin daily. On June 10, 1977, serum electrolytes were normal and serum salicylate was 13.8 mg/100 ml.

Case 2—A 75-year-old hypertensive, nondiabetic woman had required 100 to 150 mg of dichlorphenamide per day for chronic open-angle glaucoma, and 975 mg of aspirin four to five times daily for chronic

osteoarthritis for several years. In February 1975, during a hospital stay for tibial osteotomy, serum electrolytes were: sodium, 136 mEq/liter; postassium, 3.5 mEq/liter; chloride, 111 mEq/liter; and CO_2, 19 mEq/liter. On Aug. 26, 1975, after trial therapy with ibuprofen, the patient began taking 650 mg of buffered aspirin four times a day in addition to her usual aspirin dosage. From Sept. 4 to Sept. 14, 1975, she exhibited, in order of occurrence, the following symptoms: withdrawal, refusal to eat, memory lapses, confusion, disorientation, tachypnea, and unresponsiveness. On Sept. 14, 1975, she was admitted to the hospital deeply comatose and unresponsive to pain. Vital signs were unremarkable except for shallow respirations of 32 per minute. Neurologic examination revealed flaccid paralysis with absent gag and corneal reflexes, but a flexor plantar reflex. Serum chemistry values included: sodium, 152 mEq/liter; potassium, 2.1 mEq/liter; chloride, 128 mEq/liter; and CO_2, 10 mEq/liter. Arterial blood gases were: pO_2, 112 mm Hg; pCO_2, 9.3 mm Hg; pH, 7.55; and calculated bicarbonate, 8.0 mEq/liter. Urinalysis showed pH 6.5 with 2+ ketones and no detectable sugar. Complete blood cell count, chest x-ray films, and electrocardiogram were normal. The following day, further laboratory studies showed: serum salicylate, 21.6 mg/100 ml; blood urea nitrogen, 16 mg/100 ml; arterial lactate, 2.8 mEq/liter; ammonia, 157 μg/100 ml (45 μg/100 ml when repeated; normal, 18 to 48 μg/100 ml); and serum barbiturates, nondetectable. An electroencephalogram was flat and without localizing value. Treatment consisted of discontinuation of dichlorphenamide and aspirin, and intravenous fluids and potassium replacement. The patient regained consciousness, without neurologic sequelae, during a three-day period, concurrent with resolution of her acid-base and electrolyte disturbance. Neurologic consultants agreed with the diagnosis of metabolic imbalance and salicylate intoxication. When last seen on April 21, 1977, she was well and was taking 4.8 g of aspirin daily, but no dichlorphenamide.

DISCUSSION

The tinnitus and hyperventilation in the patient in Case 1 and the severe respiratory alkalosis, metabolic acidosis, and profound central nervous system disturbance in the patient in Case 2 are classical signs and symptoms of salicylate intoxication. Salicylates exert many of their toxic effects on or via the central nervous system.[1,3,5,7,8] Rats dying from varying salicylate doses administered by various routes demonstrate considerable variability in the length of time from drug administration to death, and considerable variability in blood, muscle, and liver salicylate levels, but little variability in brain salicylate concentration.[5] This suggests that the rats die when a critical brain salicylate level is reached,[5] and is consistent with the poor correlation between serum salicylate levels and clinical severity of salicylate intoxication in humans.[5,7,9]

Salicylic acid has a pK′ of 3, and is thus highly ionized (99.996%) at normal blood pH of 7.4.[5] A small change in blood pH causes a large change in blood concentration of the nonionized form. Thus, a fall in blood pH from 7.4 to 7.2 will double the proportion of nonionized salicylic acid molecules from 0.004% to 0.008%.[5] Because ionizable drugs penetrate biologic membranes primarily in their nonionized form,[5,8] acidemia should enhance the penetration of salicylate from blood and extracellular fluid into central nervous system and other cells.[1,3,5,8] This has been demonstrated in experimental animals,[5,8,10] and probably explains why in salicylate poisoning in adult humans, acidemia is associated with impaired consciousness and carries a grave prognosis.[11]

Markedly sublethal doses of carbonic anhydrase inhibitors significantly increase the lethality of salicylate in mice[3] and rats,[8,12–14] presumably because of the carbonic anhydrase inhibitor-induced acidemia. Thus, although carbonic anhydrase inhibitor-induced alkalinization of the urine increases renal clearance of salicylate,[1,3,5,7] authors who acknowledge the potential value of carbonic anhydrase inhibitors in treatment of salicylate intoxication stress the need to prevent acidemia by intravenous administration of bicarbonate.[1,3,5,8] Our patient in Case 2 had had mild acidemia, probably carbonic anhydrase inhibitor-induced, which had been noted during a routine hospital admission for a tibial osteotomy seven

months before her profound salicylate intoxication.

To our knowledge, these are the first such occurrences of apparent salicylate intoxication reported in patients receiving carbonic anhydrase inhibitor therapy for glaucoma and chronic aspirin therapy for arthritis. Because of recent advances in the understanding of aspirin's effects on prostaglandin synthesis[15] and platelet function,[16] there soon may be a marked upsurge in its therapeutic use, even if only on a trial basis, in a wide variety of ocular and systemic diseases.[17–26] The cases described here should re-alert ophthalmologists and other physicians to the potential hazard of combining high-dose aspirin therapy with carbonic anhydrase inhibitor therapy. In patients requiring such combined therapy, low doses of methazolamide (which cause little or no systemic acidosis),[27] oral sodium bicarbonate,[1,3,4,5,8] or both, should theoretically decrease the risks of severe toxicity.

SUMMARY

A 67-year-old woman and a 75-year-old woman taking carbonic anhydrase inhibitors for therapy of glaucoma and high doses of aspirin for therapy of arthritis developed severe acid-base imbalance and salicylate intoxication. Neither patient exhibited ill effects when taking high aspirin doses without carbonic anhydrase inhibitor. Carbonic anhydrose inhibitor-induced acidemia increases the risk of developing salicylate intoxication in patients receiving high aspirin doses.

ACKNOWLEDGMENT

Peter A. Duehr, M.D., referred Case 2.

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OPHTHALMIC MINIATURE

This kind of eyeball-to-eyeballing, though often amiable, should not be confused with eyeballing, eyeball analysis, or eye contact. The baritone Sherrill Milnes has told an interviewer that he is able to sing a score after eyeballing it. The action here is unilateral. The score does not eyeball back. Eyeball analysis takes place when archeologists dig up artifacts and look at them with the naked eye. However, most archeologists consider it infra dig and prefer to use instruments, even though it was *on* an infra dig that one of the most important infrastructures of an ancient civilization was found.

Edwin Newman, *A Civil Tongue*
New York, Warner Books, 1977

VARIX OF THE OPTIC DISK

LEONARD JOFFE, F.R.C.S.ED., WILLIAM H. ANNESLEY, JR., M.D.,
JERRY A. SHIELDS, M.D., AND JAY L. FEDERMAN, M.D.
Philadelphia, Pennsylvania

Aneurysmal dilatations of the retinal vessels have been described in Coats' disease and related telangiectasias,[1] von Hippel's angiomatosis retinae,[2] cavernous hemangioma of the retina,[3] and in retinal macroaneurysms.[4] In retinal macroaneurysms the dilatation occurs in the larger retinal arteries, usually within the first three orders of bifurcation.[4] Thrombosis of the macroaneurysm, pulsation, and delayed filling on fluorescein angiography have been described.[5] In Coats' disease and the closely related Leber's miliary aneurysms, and in von Hippel's disease and cavernous hemangioma of the retina, the dilatations generally occur in smaller vessels that may be of arterial or venous origin.[1]

We describe herein unusual saccular vascular dilatation on the optic disk, occurring in an asymptomatic patient. We have termed this lesion "varix of the optic disk."

CASE REPORT

A 74-year-old woman was referred here for a recent posterior vitreous detachment and peripheral retinal hole in her left eye. The referring physician had also noted a vascular dilatation on the optic disk, which had not been noted at a routine examination one year previously. Her medical history was unremarkable. The blood pressure was 100/60 mm Hg. Ocular examination revealed a corrected visual acuity of 6/6 (20/20) in both eyes, and normal intraocular pressures. The external examination and anterior segment in both eyes and the fundus examination of the right eye were normal.

The left eye showed a posterior vitreous detachment with collapse and a round retinal hole with free-floating operculum at the 2 o'clock meridian in the peripheral retina. On the center of the optic nerve head and overlying the central retinal vessels was a saccular dilatation, filled with dark red blood, similar in appearance and color to the retinal veins (Fig. 1). No pulsation was noted. There were no signs of venous stasis in the retina, which appeared normal.

Fluorescein angiography at this time revealed normal retinal vascular flow dynamics. The lesion was isolated from the retinal circulation and did not fill with fluorescein at any stage of the study. In the recirculation phase there was some hyperfluorescence in the inferior portion of the varix (Fig. 2).

Four months later the patient was still asymptomatic. Clinical examination of the lesion showed a slight decrease in size of the saccule, and sedimentation of red blood cells had occurred within it, leaving a layer of red blood cells below and clear fluid above (Fig. 3). Fluorescein angiography at this time showed initial hypofluorescence of the lesion, but slow filling occurred late in the venous phase, probably from the central retinal vessels or one of their immediate branches. Late frames showed intense fluorescence of the superior three fourths of the lesion, with nonfluorescence below. This layering corresponded to the red blood cell sedimentation seen clinically (Fig. 4).

No treatment was advised, and we have continued to observe the patient.

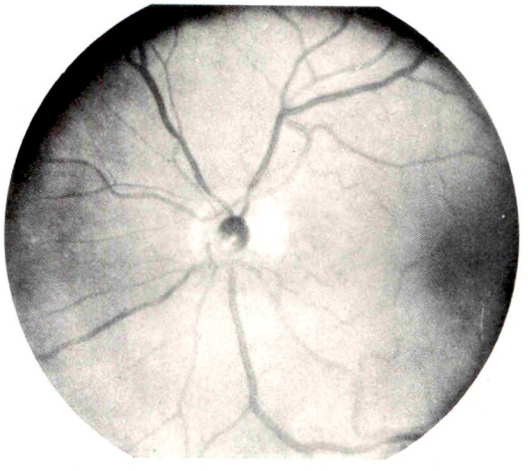


Fig. 1 (Joffe and associates). Fundus photograph in September 1977, showing large vascular dilatation in the center of left optic disk.

From the Retina Service, Wills Eye Hospital, Philadelphia, Pennsylvania. This study was supported in part by the Retina Research and Development Foundation, Philadelphia, and the Lions Club of Pennsylvania.

Reprint requests to Jerry A. Shields, M.D., Retina Service, Wills Eye Hospital, 1601 Spring Garden St., Philadelphia, PA 19130.

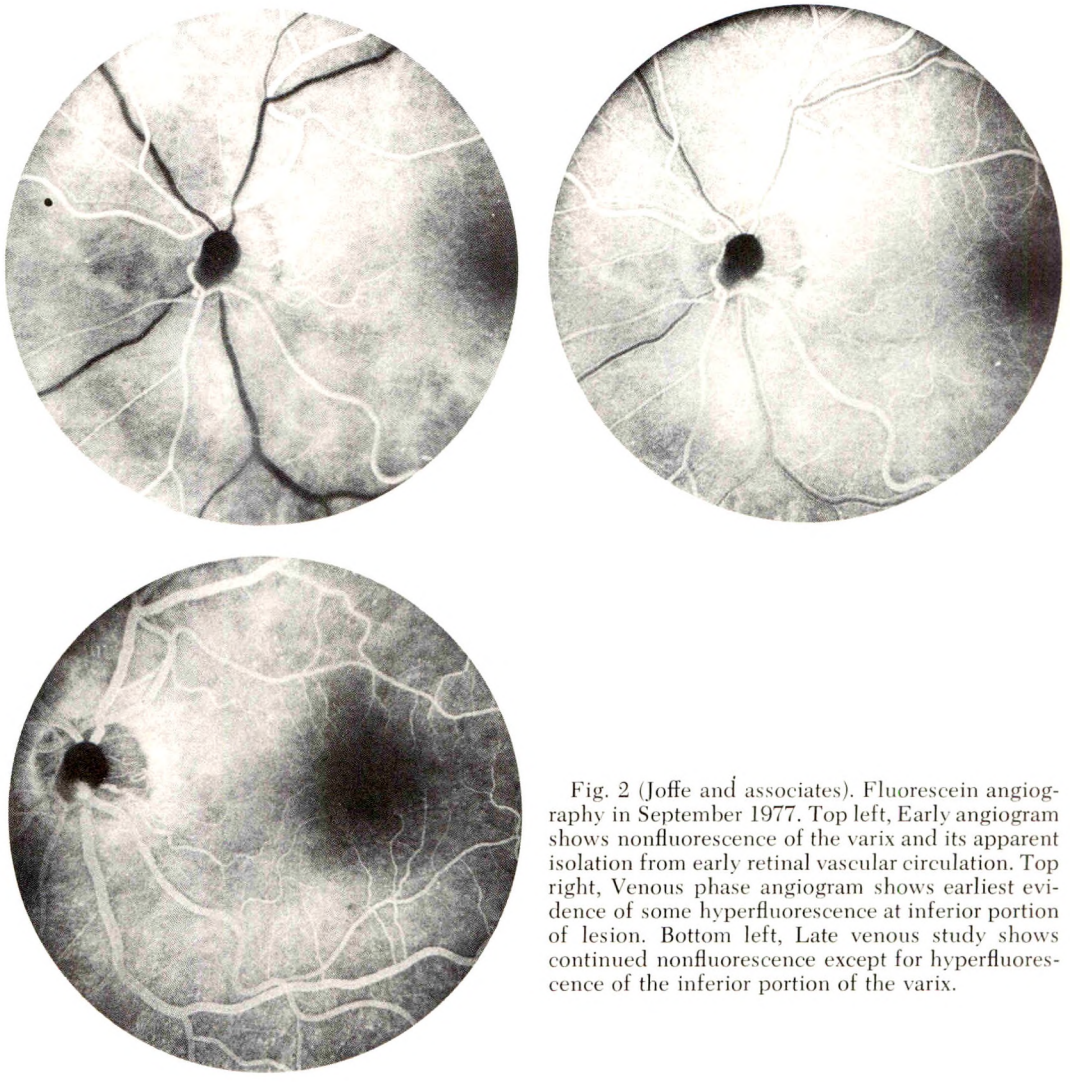


Fig. 2 (Joffe and associates). Fluorescein angiography in September 1977. Top left, Early angiogram shows nonfluorescence of the varix and its apparent isolation from early retinal vascular circulation. Top right, Venous phase angiogram shows earliest evidence of some hyperfluorescence at inferior portion of lesion. Bottom left, Late venous study shows continued nonfluorescence except for hyperfluorescence of the inferior portion of the varix.

Discussion

The relatively large vascular dilatation on the optic nerve head of this patient neither caused any symptoms nor resulted in disturbance of any aspect of the retinal circulation. The lesion demonstrated relative isolation from the retinal circulation, evidenced by the sluggish flow of fluorescein into it in the later phases of the study. Further evidence of

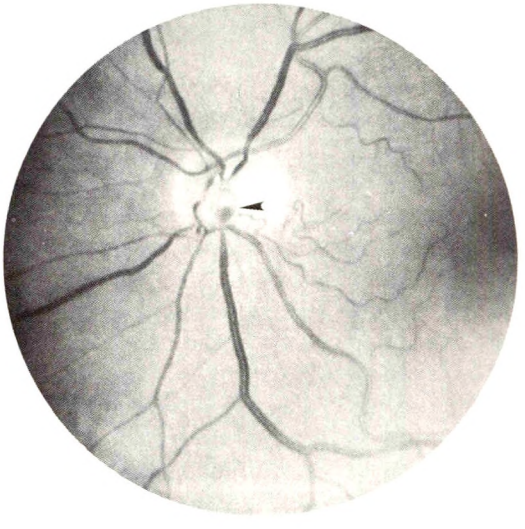


Fig. 3 (Joffe and associates). Fundus photograph in January 1978, showing slight decrease in size of the lesion and a layering effect with sedimentation of red blood cells to the inferior portion (arrow).

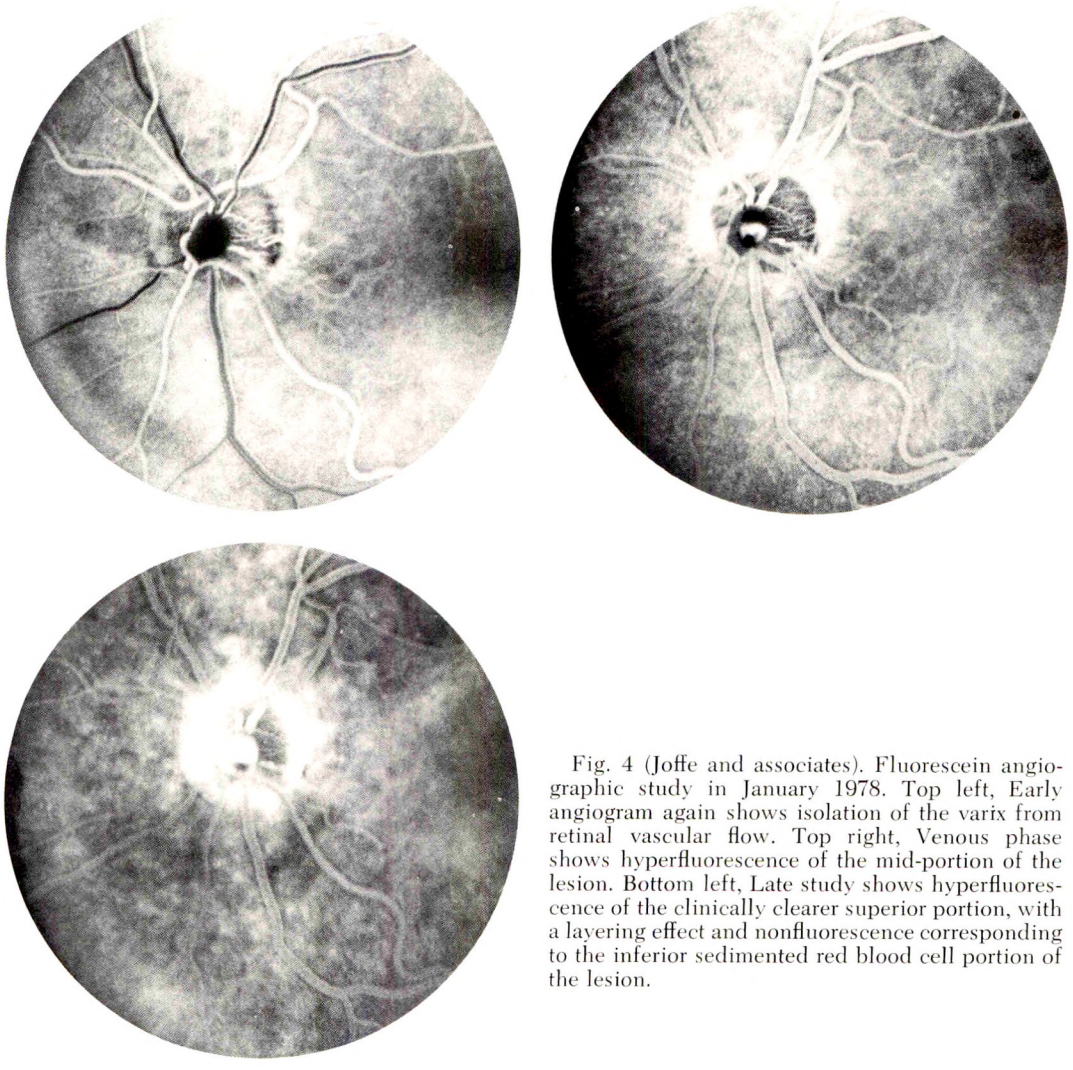


Fig. 4 (Joffe and associates). Fluorescein angiographic study in January 1978. Top left, Early angiogram again shows isolation of the varix from retinal vascular flow. Top right, Venous phase shows hyperfluorescence of the mid-portion of the lesion. Bottom left, Late study shows hyperfluorescence of the clinically clearer superior portion, with a layering effect and nonfluorescence corresponding to the inferior sedimented red blood cell portion of the lesion.

stagnation of blood within the lesion is the sedimentation of red blood cells, giving a layering effect, which resembles the clinical and angiographic appearance of the individual saccules in cavernous hemangioma of the retina.[3]

We believe the saccular dilatation is probably derived from the central retinal vein or one of its tributaries on the optic nerve head. It appeared clinically and angiographically separate from the arterial tree and was similar in color to the retinal veins. It is also theoretically possible that an arterial macroaneurysm, associated with stasis, could have the same appearance. However, retinal macroaneurysms usually fill in the arterial phase of fluorescein angiography and are often accompanied by exudation or retinal or vitreous hemorrhage, and the patients are often hypertensive.[4–7]

In view of the probable venous, but still uncertain origin of this unusual lesion, and its apparent isolation from the main retinal circulation, we have termed it a "varix of the optic disk." The develop-

ment of this lesion since a previous routine examination and the subsequent reduction of size on follow-up examination suggest an acquired weakness in the vessel wall, leading to a saccular dilatation. The stasis within it may have resulted in thrombosis and gradual reduction in size.

Summary

A 74-year-old woman had a saccular dilatation, presumably of the central retinal vein, on the optic nerve head. The lesion caused no symptoms, and over a four-month period showed evidence of thrombosis and stagnation within it. The lesion caused no interference with either the arterial or venous circulation of the retina. We advised no treatment and continue to observe the patient.

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BILATERAL OPTIC NERVE HYPOPLASIA WITH NORMAL VISUAL ACUITY

ÅKE BJÖRK, M.D., C.-G. LAURELL, M.D., AND ULLA LAURELL, M.D.
Stockholm, Sweden

Optic nerve hypoplasia is a congenital defect of one or both optic nerves. Often reported as an isolated anomaly, it may also be combined with malformations of the forebrain, such as agenesis of the septum pellucidum and malformation of the chiasm.[1] Combinations with ocular anomalies such as microphthalmos and aniridia[2] have also been described.

In the past optic nerve hypoplasia was assumed to be an uncommon defect, but recently some authors have reported series of cases: Edwards and Layden,[3] 1970 (25 cases); Walton and Robb,[4] 1970 (20 cases); Krystkowa, Mirkiewicz-Sieradzka, and Bryk,[5] 1975 (seven cases); and François and De Rouck,[6] 1976 (22 cases). With one exception, all patients had profoundly reduced visual acuity, and in several cases the eye involved was almost or totally blind. The exception was a patient with visual acuity of 6/15 (20/50) in the affected eye.

Since Schwarz[7] described a case of optic nerve hypoplasia in 1915, similar cases have been described.

Because most of the patients described were young or mentally retarded, it often has not been possible to determine their visual functions, especially in the examination of the visual fields.

In the few cases in which perimetry was performed, different types of defects have been reported, often combined with a general narrowing of the fields. Nasal defects are the most common. Schwarz[7] reported a case of an 18-year-old girl with bilateral optic nerve hypoplasia. Corrected visual acuity was 6/12 (20/40) in each eye. Visual fields were reduced in all directions with an almost total loss of the nasal halves. Missiroli[8] described three siblings with bilateral optic nerve hypoplasia. Two sisters, 20 and 18 years old, and their 8-year-old brother had binasal hemianopia. The elder sister had corrected visual acuity of 6/9 (20/30) in each eye and esotropia. The younger sister had corrected visual acuity of R.E.: 6/9 (20/30); L.E.: 6/7.5 (20/25). The brother also had esotropia and low visual acuity. Manor and Korczyn[9] reported a case of unilateral involvement in a 53-year-old woman with corrected visual acuity in the affected eye. This field was constricted with a large defect in the nasal parts. Some other authors[10–12] also reported nasal defects.

Temporal or mainly temporal loss has been described in only a few cases. Berggren[13] reported a case of a 7-year-old girl with esotropia and poor vision in her right eye. The visual acuity was less than 6/60 (20/200) and the visual field was seriously impaired. Only a small part of the nasal field was left. Ellenberger and Runyan[1] described a 23-year-old woman dwarf with frontal headache, dizziness, poor vision, and nystagmus. Visual acuity was R.E.: 6/60 (20/200); L.E.: 6/7.5 (20/25). Visual fields revealed a bitemporal loss. Pneumoencephalography demonstrated that the septum pellucidum was absent and the frontal horns were fused into a common chamber. A case not unlike the one just described was reported by Harrington.[14] An 18-year-old girl with nystagmus and eye muscle palsies had visual acuity of 6/9 (20/30) in each eye and a bitemporal loss in the fields. She had an apparent decrease of retinal nerve fiber bundles in the nasal retina of each eye. Pneumoencephalography was not performed.

From the Department of Ophthalmology, Karolinska Hospital, Stockholm, Sweden.
Reprint requests to C.-G. Laurell, M.D., Department of Ophthalmology, Karolinska Hospital, S-104 01 Stockholm, Sweden.

Altitudinal defects in the visual fields have also been reported.[15,16]

Central or paracentral scotomas in fields with normal outer limits have also been described. Seeley and Smith[17] reported three such cases with bilateral cecocentral scotomas. One of these patients had visual acuity of R.E.: 6/15 (20/50); L.E.: 6/21 (20/70). The other two patients had poor vision.

Harmless developmental anomalies of the eye and optic nerve can sometimes cause symptoms that may be misinterpreted as a serious disease of the nervous system. This mainly concerns malformations such as tilted disk and drusen of the optic disk discovered during examinations of patients suffering from headache, dizziness, and other neurologic complaints.

We suggest that optic nerve hypoplasia may also play such a role, and we present herein three such cases to support our theory.

Case reports

Case 1—A 26-year-old man had no eye problems and was healthy until 1975, when he was admitted here because of vertigo. The vertigo was uncharacteristic and no otological cause was found. An ophthalmologic examination in 1976, however, showed defects in the lower part of the visual fields with Goldmann perimetry (Fig. 1). Visual acuity was 6/4 (± 0) bilaterally. Color vision (H-R-R pseudoisochromatic plates) was normal in both eyes. The ocular fundi showed optic disks much smaller than normal surrounded by a pale zone. Photography of the fundi with red-free light showed degeneration of retinal nerve fiber layers in the upper retina (Figs. 2 and 3). The eyes were otherwise normal. The neurologic examination revealed nothing abnormal. Pneumoencephalography showed normal conditions. The optic foramina were 4 mm in diameter on roentgenograms, that is, narrow, but still within normal limits.

Case 2—A 19-year-old man had had psychomotor epilepsia since the age of 10 years. He was employed as a messenger and had no eye problems. Since childhood he had the habit of bending his head forward when walking. He was admitted to the neurologic clinic in 1976 for an adjustment of his drug therapy. Visual acuity was 6/6 (20/20) (±0) in both eyes. Color vision was normal. Perimetry showed bilateral visual field defects (Fig. 4). Ophthalmoscopy showed optic disks smaller than normal with a peripapillary zone (Fig. 5). The eyes were otherwise normal. X-ray examination showed a 4-mm diameter of the optic foramina.

Case 3—A 55-year-old man had no eye problems. Visual acuity was normal on earlier controls. He was admitted here in 1976 because visual field defects were discovered on a routine examination. Visual acuity was 6/6 (20/20) in both eyes after correction of a moderate myopia. Perimetry showed bilateral lower visual field defects (Fig. 6). Color vision was normal. Ophthalmoscopy showed optic disks much smaller than normal. They were surrounded by a large peripapillary zone (Fig. 7). The eyes were otherwise normal. X-ray examination showed optic foramina of normal size.

Discussion

The practical importance of diagnosing optic nerve hypoplasia has usually been

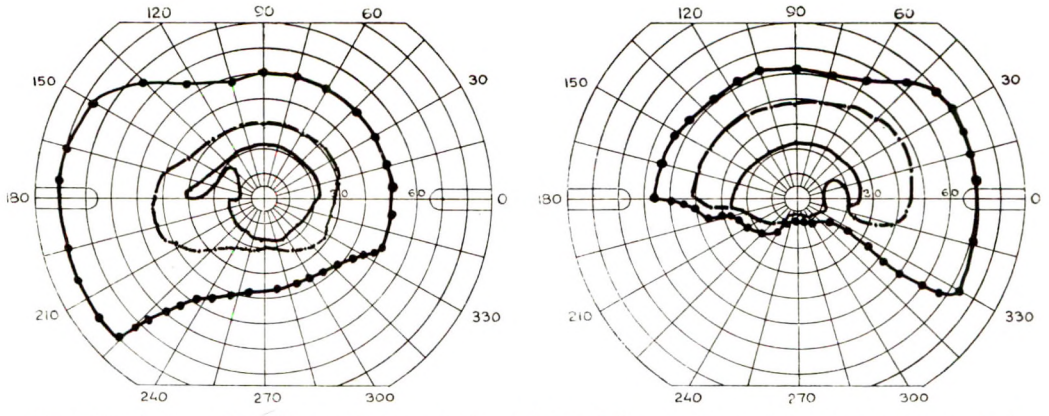


Fig. 1 (Björk, Laurell, and Laurell): Case 1. Visual fields (left and right eye) showing defects in the lower segment of both fields (Goldmann perimetry, isopters: I_4, I_2, I_1).

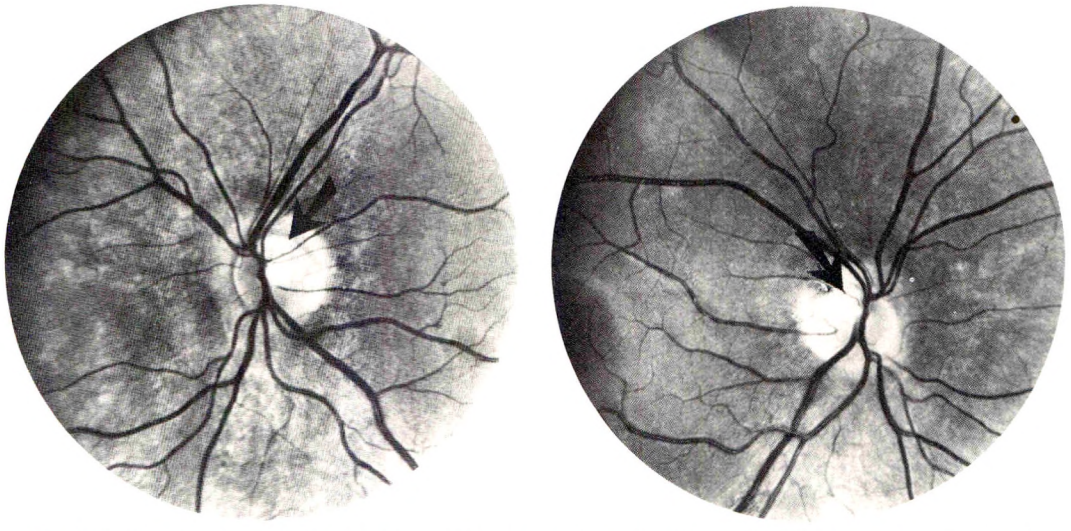


Fig. 2 (Björk, Laurell, and Laurell): Case 1. Right and left fundus. The optic disks are small and show thin pigmented edges surrounded by pale gray avascular zones. These findings may give an impression of a normal disk. (Arrows indicate limit of papilla.)

linked to the treatment of children with strabismus. If one diagnoses optic nerve hypoplasia in a child who has a heterotropia, the child and the parents can often be spared the inconvenience of occlusion therapy.[3,5] Many cases of undiagnosed optic nerve hypoplasia have been described in which occlusion therapy was used for a long time without any positive results.

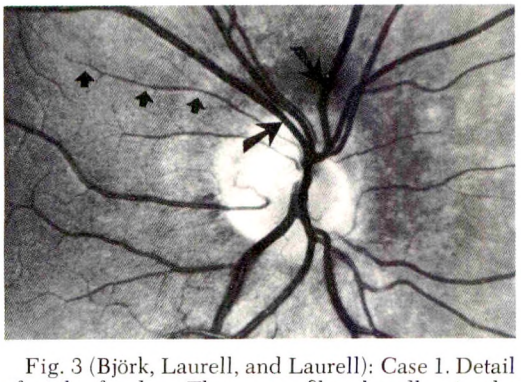


Fig. 3 (Björk, Laurell, and Laurell): Case 1. Detail of right fundus. The nerve fiber bundles in the upper retina are not clearly visible and the blood vessels appear naked. (Large arrows indicate naked blood vessels; small arrows show lower limit of the nerve fiber bundle defect.)

However, we consider that it is no longer justified to judge cases of optic nerve hypoplasia as unsuitable for occlusion therapy. We believe a short-term trial of occlusion is appropriate because hypoplasia may leave the papillomacular bundle more or less intact. Gardner and Irvine[15] described one case of right esotropia with poor vision in the squinting eye in which visual acuity improved to almost 6/9 (20/30) after occlusion therapy. These authors concluded that "since one cannot reliably predict whether or not central vision is affected from the appearance of the disk, a trial of occlusion therapy is indicated for a child with hypoplastic optic nerve and squint." This conclusion is supported by our patients, all of whom had normal vision.

More than half of the published cases of optic nerve hypoplasia are unilateral. Visual acuity of the affected eye has generally been poor, often considerably less than 6/60 (20/200). Several authors have maintained that poor visual acuity is essential for diagnosis.[3,18]

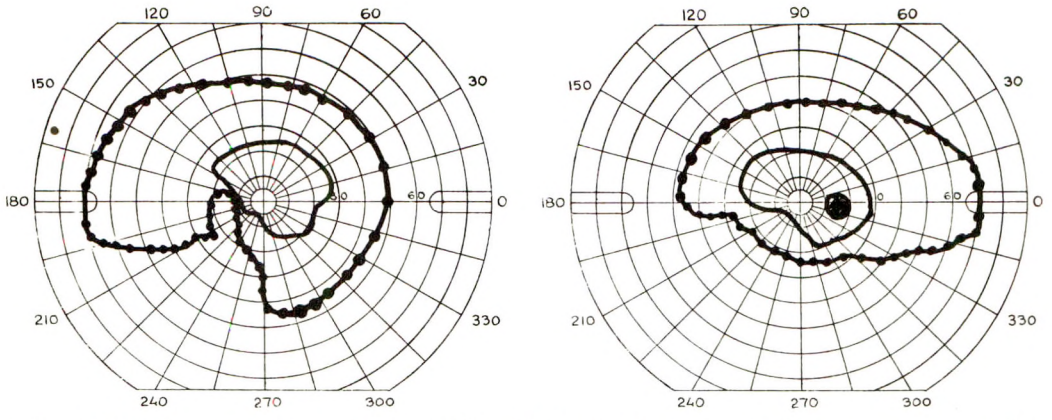


Fig. 4 (Björk, Laurell, and Laurell): Case 2. Visual fields showing defects in the lower parts of both fields (isopters: R.E., I_4, I_3; L.E., II_4, I_3).

Gardner and Irvine[15] described a girl, treated for esotropia, who had bilateral optic nerve hypoplasia, but normal visual acuity of 6/6 (20/20) in each eye. Goldmann perimetry showed loss of the inferior half of each visual field. This patient was under ophthalmologic observation for many years because of her strabismus, and the optic nerve hypoplasia was diagnosed at a follow-up examination. When we examined our three patients, this case was the only one reported with normal vision in both eyes and bilateral optic nerve hypoplasia and is similar to our cases in visual acuity and visual field defects. Patients like ours, however, with no ocular problems, may escape ophthalmologic examination completely and even when examined, their cases are likely to be incorrectly diagnosed. Bilat-

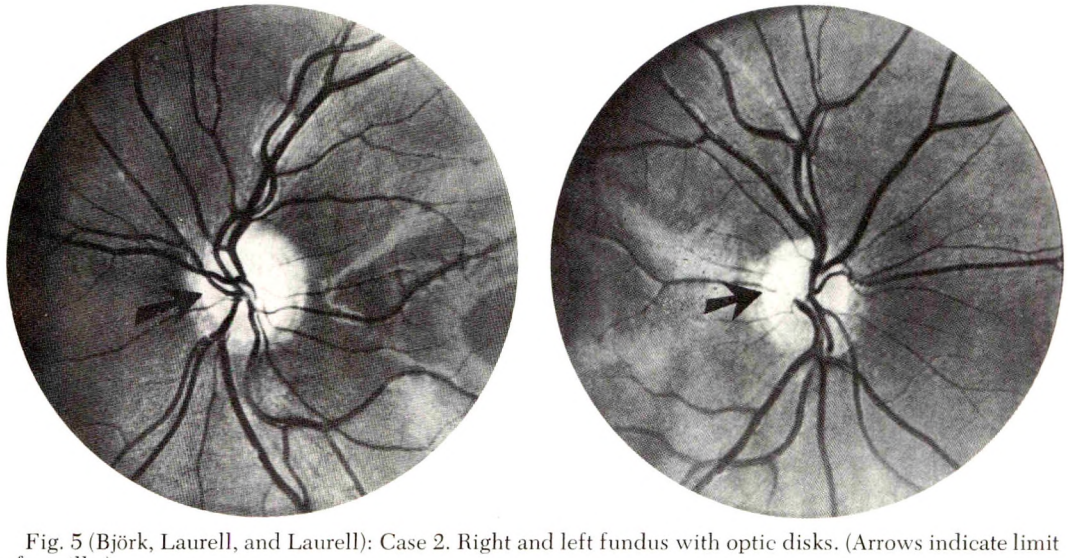


Fig. 5 (Björk, Laurell, and Laurell): Case 2. Right and left fundus with optic disks. (Arrows indicate limit of papilla.)

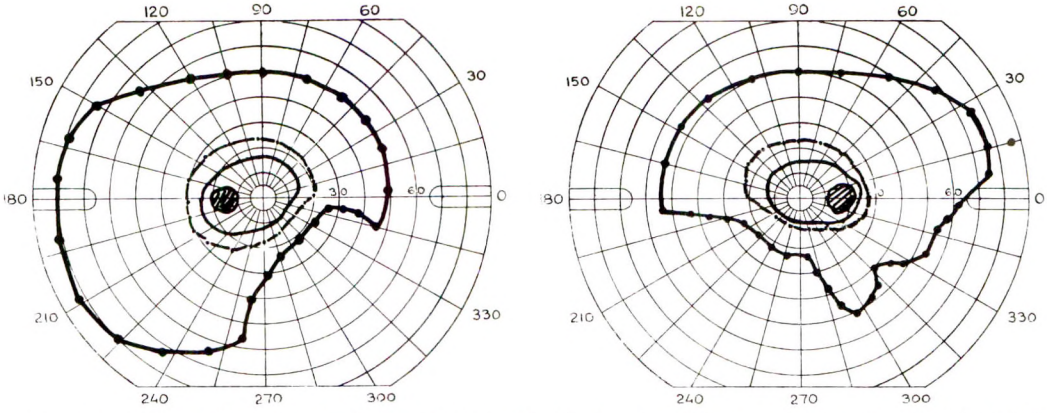


Fig. 6 (Björk, Laurell, and Laurell): Case 3. Visual fields showing defects in the lower parts of both fields (isopters: IV_4, I_3, I_2).

eral cases especially can be difficult to discover in a routine examination. The small disk combined with the surrounding circular halo may appear as a normal disk. In suspected cases, photography can be helpful. In our cases, it was not until their visual fields were checked as part of a neurologic investigation that attention was called to the anomaly of the disks. Accordingly, we may suspect that the milder forms of optic nerve hypoplasia are more common than generally assumed.

Because these patients have no difficulties in work or other daily activities, that is, they have adjusted themselves to their visual field defects over many years, these anomalies are probably congenital. One of our patients is a truck driver, another a bus driver.

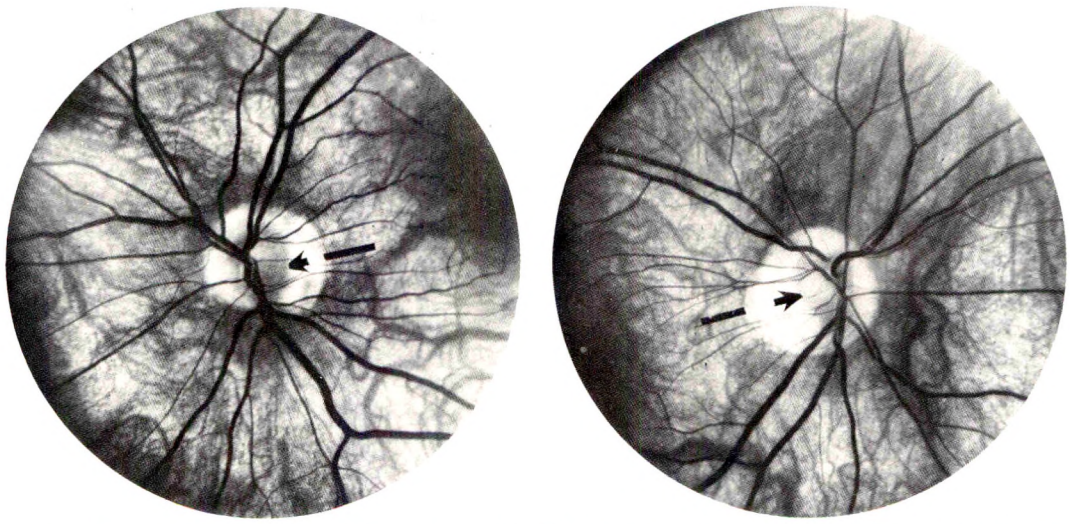


Fig. 7 (Björk, Laurell, and Laurell): Case 3. Right and left fundus. The disks are small and surrounded by pale zones. This case also shows a temporal white crescent and a thin retina caused by myopia. (Arrows indicate limit of papilla. Arrows are broken by the temporal crescent.)

Our cases indicate that the visual field defects may lead to the discovery of optic nerve hypoplasia with normal visual acuity. These defects can raise erroneous suspicion of neurologic disease and may lead to unnecessary examinations. Our three cases illustrate the difficulties in revealing optic nerve hypoplasia in bilateral cases with normal visual acuity 6/6 (20/20) or more and absence of other ocular symptoms such as strabismus.

Petersen and Walton[16] described 17 cases of optic nerve hypoplasia in children of mothers with severe diabetes. Of our three cases only one had a mother with diabetes during pregnancy. Several of these children had good vision and altitudinal or sector visual field defects resembling those found in our cases. The report supports our presumption that cases of optic nerve hypoplasia with good vision are not so uncommon as previously assumed.

Summary

A 26-year-old man, a 19-year-old man, and a 55-year-old man had bilateral optic nerve hypoplasia. They all had normal vision, but considerable defects in the inferior segments of the visual fields.

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VISUAL-EVOKED RESPONSE DIFFERENTIATION OF ISCHEMIC OPTIC NEURITIS FROM THE OPTIC NEURITIS OF MULTIPLE SCLEROSIS

W. BRUCE WILSON, M.D.

Denver, Colorado

Ischemic optic neuritis is the most common type of optic neuritis in people over 60 years of age. A diagnosis of ischemic optic neuritis is strongly suggested when recovery of vision is minimal and a vascular disease is present, for example, in temporal arteritis, diabetes mellitus, or hypertension. The optic neuritis of multiple sclerosis is the most common type of optic neuritis in patients 20 to 40 years of age. Return of vision to a near normal level in the absence of vascular disease is indicative of this entity. However, in any given patient in the fifth or sixth decade of life, the differentiation between the two types of optic neuritis may be difficult.

Because of the diagnostic value of the visual-evoked response in multiple sclerosis, we studied it in 15 patients with ischemic optic neuritis. The most reliable change in the visual-evoked response in the optic neuritis of multiple sclerosis seems to be an increase in the latent period. This is most consistently recognized in the first negative wave and the major positive wave.[1-6] The latent period is the period of time between stimulus to the retina (for example, a flash of light) and the response (potential change) of the occipital cortex. An increase in the latent period may be seen in multiple sclerosis even without symptoms or signs of optic neuritis.[5] To my knowledge, no study has been published defining the visual-evoked response findings in ischemic optic neuritis.

From the Division of Ophthalmology, Denver General Hospital, and Division of Ophthalmology, University of Colorado Medical Center, Denver, Colorado.

Reprint requests to W. Bruce Wilson, M.D., Division of Ophthalmology, Denver General Hospital, West 8th Ave. and Cherokee St., Denver, CO 80204.

SUBJECTS AND METHODS

I studied 15 patients with unilateral ischemic optic neuritis to determine if characteristic changes had occurred in the visual-evoked response. The age range was 52 to 79 years. Each patient had had a sudden loss of vision in one eye and had not shown significant visual improvement. Excluded from the study were those patients who had more than one line of improvement in Snellen vision or a field defect that disappeared with time and all patients with clinically suspected strokes. Each patient had a loss of central vision, some mild (6/7.5 [20/25]), some severe (6/120 [20/400]). Each had a defect in the field of vision consistent with ischemic disease, namely, altitudinal defect or nerve fiber bundle defect. Twelve of the 15 patients showed acute changes at the disk head. These changes were edema, hemorrhage, dilated tortuous veins, and nerve fiber layer microinfarcts. All had a diagnosis suggesting an ischemic etiology for the acute optic nerve damage: temporal arteritis, diabetes mellitus, collagen vascular disease, or hypertension.

Fifty individuals who were free of disease served as control subjects. Both groups were examined in the same way.

The patients were seated in a semidarkened room (background light intensity of approximately one foot candle), with their eyes open and pupils dilated (tropicamide 1%). Gold-plated electrodes were affixed to the scalp with electrode paste. The visual-evoked response was recorded from the active 0_1 and 0_2 electrodes; linked ears served as reference (10-20 international nomenclature). The forehead served as ground. The resistance between the active and reference electrodes was kept under 3,000 ohms.

Two methods of stimulation were used: a diffused flash of light and a reversing checkerboard pattern. The diffused light was delivered by a Grass PS 22 photostimulator of 13-cm diameter, fitted with a diffusing screen that delivered approximately 250,000 candles/m^2. The diffused flash of light was displayed at 0.33 meter and the checkerboard pattern at 1 m. In both cases a small, nonluminous fixation target was used. One hundred stimuli (1/sec) were given with each method. The checkerboard pattern was displayed over a field of 30 degrees on a side using large checks, 1 degree on a side. The black and white checks were displayed continuously, reversed on stimulus, produced a constant luminance background, and had values of 50 and 750 candles/m^2, respectively.

The cortical evoked responses were amplified by a Grass Model VIII electroencephalograph (band width, 1 to 70 Hz) coupled to a buffer amplifier. A signal averager was used to accumulate the amplified cortical responses. The final averaged wave was displayed on a Tektronic scope and photographed with a Polaroid camera. Analysis time was 250 msec. Auditory masking was used. The first five peaks were analyzed for three factors: latency, amplitude, and amplitude-latency ratio.

Each patient had a complete neuro-ophthalmic examination. This included best corrected Snellen vision; Hardy, Rand, and Rittler color vision; Pulfrich phenomenon; formal field of vision; pupil examination; and a dilated examination of the posterior pole. Laboratory examination included a complete blood cell count, an erythrocyte sedimentation rate, rheumatoid arthritis factor, antinuclear antibody test, serology test for syphilis, glucose tolerance, triglycerides, cholesterol, and coagulopathy profile in all patients.

Whole retina and macular electroretinograms were done in each patient to demonstrate that the retina was not the cause of the abnormality in the visual-evoked response.

Results of normative data, diffused light—Values were similar to those reported by Kooi[7] and Richey.[8] Measurements for latency were always made from the beginning of stimulation to a positive or negative peak on the wave. The first peak in our laboratory was negative. The following peaks were positive, negative, positive (major positive), and negative, respectively. The upper limit of normal for each peak (mean + 3 SD) was: first negative, 60 msec; first positive, 85 msec; second negative, 100 msec; second or major positive, 120 msec; and the third negative, 150 msec. The first negative and major positive wave peaks were chosen for data reporting; they were thought to be representative. The range of amplitude for the first negative peak was 3 to 15 μV (mean, 8 μV), and 8 to 40 μV (mean, 24 μV) for the major positive peak. The amplitude for the first negative peak was measured from the baseline to the top of the peak. For the major positive peak, amplitude was measured from the previous highest point on the wave.

Results of normative data, checkerboard pattern—Data for pattern stimulation was similar to those of Halliday[3,4] and Asselman.[1] The upper limit of normal (mean + 3 SD) was 60 msec for the first negative peak and 95 msec for the major positive peak. The range of amplitude was 4 to 12 μV (mean, 7 μV) and 10 to 30 μV (mean, 18 μV), respectively. Amplitude was measured as it was when diffused light was used.

Most patients displayed a five-peak wave (Fig. 1) when stimulated by the diffused light method, but a three-peak wave (Fig. 2) when stimulated by the checkerboard pattern method. We included data only on those patients with a five-component wave on diffused light

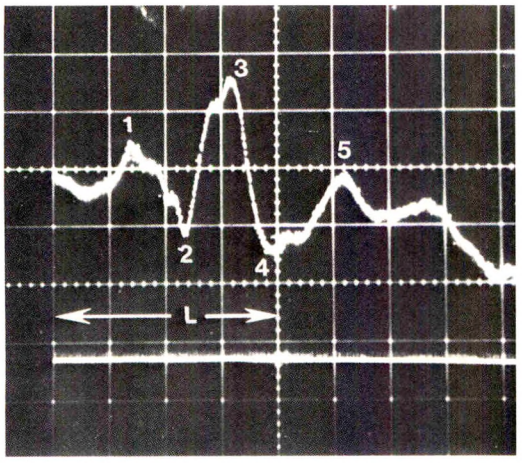


Fig. 1 (Wilson). A normal five-peak visual-evoked response wave obtained by stimulating the eye with a diffused flash of light. All figures have the same recording format; negative is up, each x-axis major division represents 30 msec time, each y-axis major division represents 10-μV amplitude, and the stimulus is at the beginning of the trace pattern. "L" indicates latent period of major positive peak. The five peaks are numbered 1 (first negative), 2 (first positive), 3 (second negative), 4 (major positive), and 5 (third negative).

stimulation and a three-component wave on pattern stimulation.

Results in ischemic optic neuritis patients—The first negative peak was present in 14 of the 15 patients. It increased in the latent period (diffused light and pattern) in four of the 15 patients, but was only slightly delayed in two of the four. The major positive peak (diffused light and pattern) also showed minor increases in the latent period in four of 15 patients, namely, above the mean + 3 SD (Table).

In 13 of 15 patients, the amplitude was less than 50% of the mean for the normal subjects. This was seen in the first negative peak and in the major positive peak (Table). Amplitude was inversely proportional to two factors: as the degree of involvement of central vision increased, amplitude decreased; as the area of involvement of the field of vision increased, amplitude decreased (Table).

Next, the amplitude:latency ratio was determined. Normal calculated values were 9 μV/60 msec = 0.15 for the first negative peak (diffused light and pattern), 24 μV/120 msec = 0.2 for the major positive peak (diffused light), and 18 μV/95 msec = 0.19 for the major positive peak (checkerboard pattern). Small values were consistently seen in our patients with ischemic optic nerve disease. Eight of 15 had values of 0.1 or lower for both the first negative and major positive peaks (Table). In contrast, only 10% of our

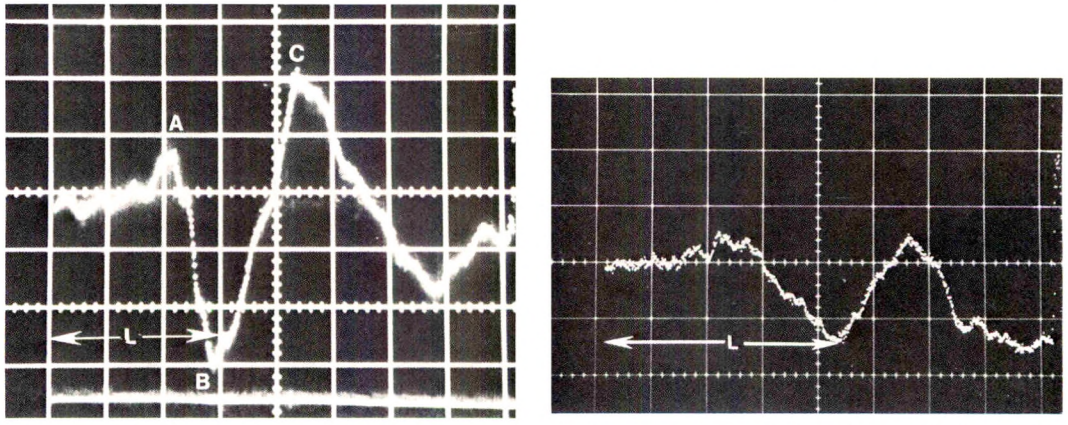


Fig. 2 (Wilson). Left, A normal three-peak visual-evoked response wave obtained by stimulating with a checkerboard pattern of 30 degrees field and checks of 1 degree on a side. The three peaks are lettered A (first negative), B (major positive), C (second negative). Right, A delayed response, as seen in multiple sclerosis, is shown for comparison. "L" indicates latent period of major positive peak.

TABLE

ANALYSIS OF 15 PATIENTS WITH UNILATERAL ISCHEMIC OPTIC NEURITIS

	Case No.	Visual Status	Latency (msec)		Amplitude (μV)		Amplitude:Latency	
			Diffused Flash	Large Field Pattern	Diffused Flash	Large Field Pattern	Diffused Flash	Large Field Pattern
Normal nerve	15 control eyes	All 6/6 (20/20) All full field of vision	All<120	All<95	Mean	Mean	Mean	Mean
Major positive peak					24	18	0.20	0.19
Diseased nerve	1	6/9 (20/30) Both had nerve fiber defect	117	94	16.1	13.0	0.14	0.14
Major positive peak	2	6/12 (20/40)	118	93	15.5	12.3	0.13	0.13
	3	6/7.5 (20/25) All had altitudinal defect	117	95	9.5	8.5	0.08	0.09
	4	6/9 (20/30)	118	95	8.5	7.5	0.07	0.08
	5	6/7.5 (20/25)	120	95	9.5	8.0	0.08	0.07
	6	6/12 (20/40)	124	100	5.5	5.0	0.04	0.04
	7	6/7.5 (20/25)	120	94	9.5	7.0	0.08	0.06
	8	6/12 (20/40)	117	93	7.5	8.5	0.06	0.09
	9	6/9 (20/30)	116	95	9.5	8.0	0.08	0.07
	10	6/30 (20/100)	120	95	9.0	8.0	0.08	0.08
	11	6/60 (20/200)	120	95	7.5	7.0	0.06	0.07
	12	6/120 (20/400)	130	102	7.5	6.0	0.06	0.06
	13	6/12 (20/40) All had depressed, contracted field	135	105	4.0	3.0	0.03	0.03
	14	6/30 (20/100)	132	104	3.5	2.5	0.03	0.02
	15	6/120 (20/400)	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen

patients with multiple sclerosis had values of 0.15 or lower for the major positive peak (diffused light or pattern).

In all 15 patients, stimulation of the normal eye always produced a normal visual-evoked response. Occasionally, the difference between results produced by stimulation of the normal or diseased eye was moderate, but usually the difference was striking (Fig. 3).

Discussion

In the 15 patients with ischemic optic neuritis, an increase in the latent period was noted, but not as often or in the amount seen in our patients with the optic neuritis caused by multiple sclerosis. Results were the same for checkerboard pattern or diffused light stimulation.

In the ischemic optic neuritis patients, amplitude was reduced more frequently than latency was increased. By looking at the amplitude column for the major positive wave in the Table, one can appreciate the value of the factor. In our series of more than 100 multiple sclerosis patients, no significant change in amplitude was seen unless visual acuity was less than 6/30 (20/100) and the field of vision was significantly altered. Even then amplitude was usually one half the mean of normal subjects. This might be compared with the two patients in this study who had less than 6/30 (20/100) vision and a generally depressed and contracted peripheral field; one had no visual-evoked response that could be measured and the other had an amplitude one fourth the normal mean. The central 10 degrees of the visual field produces most of the visual-evoked response amplitude, at least with pattern stimulation.[1] All of our 15 cases that had a marked reduction in amplitude, except for one, had either poor central vision, dense defects in the field inside 10 degrees, or both.

As shown in the amplitude:latency ratio, amplitude was also reduced proportionally more than latency was prolonged (Table). Several methods of calculating amplitude:latency ratio were considered, but because most amplitudes were close to the mean, normal seemed to be the logical amplitude factor to use. Little difference was seen in using either the mean or the mean + 3 SD as the latency factor. The latter was chosen for reporting. In some cases, when both amplitude and latency were changed to a small degree, the ratio was helpful. A low figure sug-

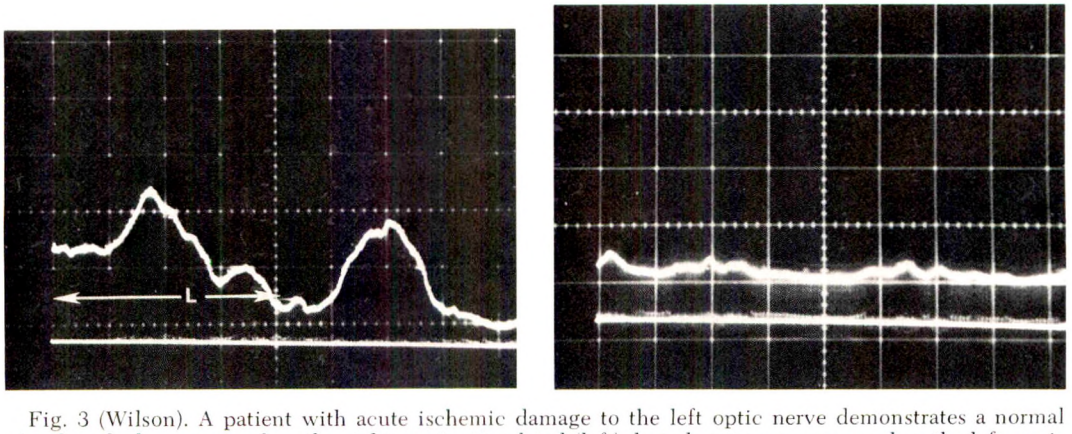


Fig. 3 (Wilson). A patient with acute ischemic damage to the left optic nerve demonstrates a normal visual-evoked response when the right eye is stimulated (left), but almost no response when the left eye is stimulated (right). (Patient had 6/30 [20/100] central vision and a dense altitudinal defect). "L" indicates latent period of major positive peak.

gested ischemic disease. The latency and amplitude differences between ischemic and demyelinating optic nerve disease are interesting. As mentioned above, an increase in the latent period is considered an almost constant finding in the optic neuritis of multiple sclerosis.[1-4,9] The change in multiple sclerosis may be caused by focal demyelination and conduction slowing.[10,11] Thus most fibers may be functioning (normal amplitude), but at a slower conduction velocity (an increase in the latent period). The opposite may be true in ischemic optic nerve disease: many fibers are not functioning (reduced amplitude) but those that are functioning are doing so at a normal conduction velocity (normal latency).

One of the most striking differences between ischemic and demyelinating disease of the optic nerve was seen when the normal eye was stimulated. In ischemic disease, the response was always normal; in the optic neuritis of multiple sclerosis, it is rarely normal. This may represent the more diffuse nature of the visual system involvement in multiple sclerosis.

In all 15 patients, an alternative method of pattern stimulation was tried. A small field of 5 degrees (with small checks of 15 on a side) was used to achieve macular stimulation. The amplitude obtained was directly proportional to the drop in Snellen vision. By the time visual acuity was reduced to 6/30 (20/100), the visual-evoked response was essentially absent.

Summary

Fifteen patients with ischemic optic neuritis studied electrophysiologically had a characteristic change of marked reduction in the amplitude of the visual-evoked response even when loss of vision was moderate. The optic neuritis of multiple sclerosis rarely produced this change. Occasionally, small increases in the latent period of the visual-evoked response were recorded from the patients with ischemic optic neuritis. The optic neuritis of multiple sclerosis usually produced significant increases in the latent period. When the normal nerve was tested in patients with ischemic optic neuritis, the visual evoked response was normal. In patients with optic neuritis of multiple sclerosis, stimulation of the "normal" nerve usually produced an increase in the latent period similar to that seen when the involved nerve was stimulated.

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BILATERAL HOMONYMOUS HEMIANOPIA

EARL W. NEPPLE, M.D., RICHARD E. APPEN, M.D., AND JOSEPH F. SACKETT, M.D.
Madison, Wisconsin

Bilateral homonymous hemianopia is considered to be rare.[1-4] However, we have seen 15 patients with this visual impairment during the past four years. The visual defect results from separate lesions of the central nervous system that affect the postchiasmal visual pathways on both sides of the brain. We describe herein patients with unequivocal clinical or radiologic documentation of this condition.

SUBJECTS AND METHODS

All patients were referred to us for neuro-ophthalmic consultation. We paid particular attention to refraction and examination of pupils, ocular motility, fundi, and visual fields by kinetic Goldmann perimetry. Clinical examination was supplemented by computed axial tomography in five patients, by cerebral angiography in five patients, by technetium brain scan in seven patients, and by autopsy in two patients.

CASE REPORTS

Case 1 (GROUP 1)—A 73-year-old man received a cardiac pacemaker in 1968 following Stokes-Adams attacks. In 1970, he observed the abrupt onset of flashing lights in the vision of both eyes. Visual acuity then was 6/6 (20/20) in both eyes, and a left homonymous superior quadrantanopia was present. In 1972, the patient began complaining of vague difficulties in reading. In 1974, visual acuity remained 6/6 (20/20) in both eyes. Examination was otherwise normal except for visual fields that showed a dense right homonymous upper quadrant defect and a less dense left homonymous superior quadrant defect (Fig. 1). The patient died six months later from histiocytic malignant lymphoma. At autopsy, the brain showed infarcts of the right temporo-occipital area and of the left occipital lobe (Fig. 2). There was marked arteriosclerosis of the aorta, the coronary arteries, and the cerebral arteries.

Comment—Arteriosclerosis with secondary cerebral infarcts was the cause of the bilateral homonymous hemianopia in this man and in five other patients (Cases 1-6) and was the most common diagnostic category. Although a sequential occurrence of the homonymous field defects was documented in this patient, the history and setting indicated a simultaneous onset in most of our patients. Bilateral lesions were discovered simultaneously for the first time in 11 of our 15 patients.

Basilar artery insufficiency was considered to be the cause of the bilateral homonymous hemianopia in the two patients with ocular motility findings indicating brain stem dysfunction.[5] Kearns[6] described three patients with bilateral homonymous hemianopia caused by basilar artery thrombosis and emphasized the association of brain stem signs with the bilateral homonymous hemianopia.

Case 7 (GROUP 2)—Three weeks after closed head trauma, a 48-year-old man became increasingly lethargic and developed dilated, unreactive pupils; blepharoptosis; and impaired adduction of the left eye. Arteriography showed a large left subdural hematoma, which was operated on shortly thereafter. Neuro-ophthalmic examination 18 days after the operation showed visual acuity of 6/6 (20/20) in both eyes with normal pupils and fundi. A small left hypertropia was a residual of the left third nerve paresis. Visual fields showed a right homonymous hemianopia combined with a left homonymous superior quadrantanopia (Fig. 3). Computed tomography documented bilateral occipital lobe infarctions (Fig. 4, left). The computed tomography one section more cephalad (Fig. 4, right) showed a normal superior portion of the right occipital lobe corresponding to the left homonymous inferior quadrant of remaining vision.

Comment—This patient and two others (Cases 7-9) sustained bilateral homonymous hemianopia secondary to uncal her-

From the Departments of Ophthalmology (Drs. Nepple and Appen) and Radiology (Dr. Sackett), University of Wisconsin Medical Center, Madison, Wisconsin.

Reprint requests to Richard E. Appen, M.D., Department of Ophthalmology, University of Wisconsin Hospitals, 1300 University Ave., Madison, WI 53706.

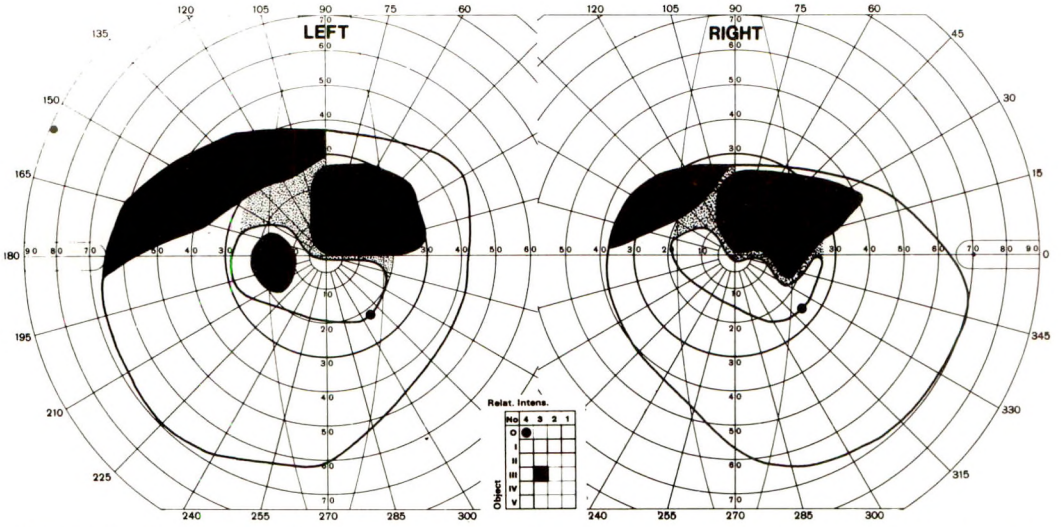


Fig. 1 (Nepple, Appen, and Sackett). Case 1. Visual field. Dense right homonymous superior quadrant and less dense left homonymous superior quadrant defect.

niation following subdural hematomas, as described by Hoyt[7] and Klintworth.[8] Incapacitating field contraction sparing only four degrees occurred in one patient who maintained visual acuity of 6/6 (20/20) (Case 9), whereas a 12-year-old boy functioned relatively well with a residual homonymous quadrant of vision (Case 8).

These infarcts result from increased intracranial pressure shifting the uncal portions of the temporal lobes downward at the tentorium, with subsequent compression of the posterior cerebral arteries against the tentorial edge. Such herniation can be caused by any expanding supratentorial lesion regardless of location. Occasionally, homonymous hemianopia may be a sign of tentorial herniation even without pupillary dilation from oculomotor nerve dysfunction.[7]

Case 10 (Group 3)—A 27-year-old woman had had severe intermittent headaches associated with nausea, vomiting, and transient dimming of vision for ten years. Five years before our examination of the patient, a left homonymous superior quadrantanopia was documented after one of these episodes. At that time, bilateral carotid arteriography was normal. Nine months before the present hospitalization, she awoke with severe headache, slurred speech,

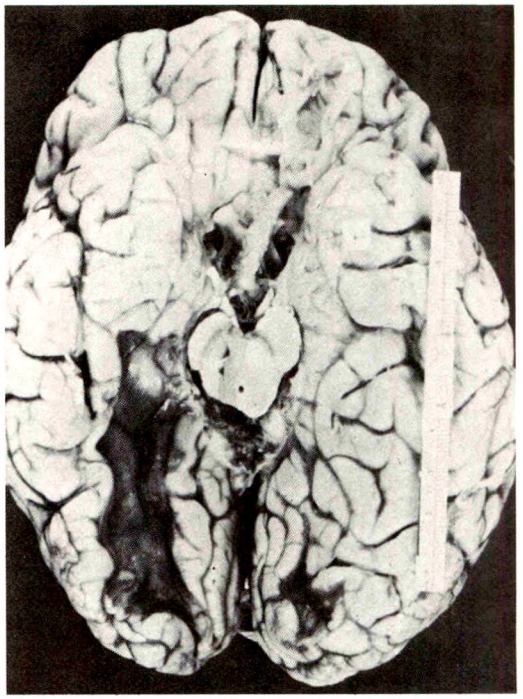


Fig. 2 (Nepple, Appen, and Sackett). Case 1. Inferior surface of brain demonstrates the old infarct in the right occipitotemporal lobes and smaller infarct in the left occipital lobe.

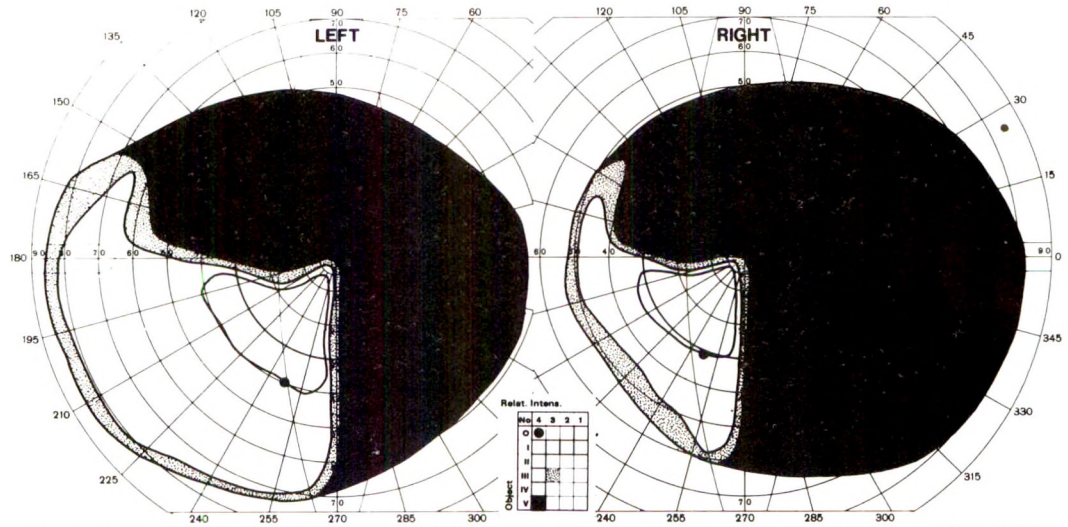


Fig. 3 (Nepple, Appen, and Sackett). Case 7. Visual field. Right homonymous hemianopia combined with left homonymous superior quadrantanopia.

and additional blurring of vision. On admission, visual acuity was 6/4.5 (20/15), and ocular motility, pupils, and fundi were normal. Visual fields showed a left superior homonymous quadrantanopia with a right homonymous superior quadrantanopia, simulating an altitudinal visual field defect (Fig. 5). Cerebral angiography showed occlusion of both posterior cerebral arteries (Figs. 6, right, and 7, right). Three years later her visual acuity was unchanged and she was otherwise well.

Comment—This woman, whose ten-year history of intermittent headache is typical of migraine, sustained permanent cerebral damage secondary to ischemia of migraine, as has been reported.[9–12] The other patient of our series with migraine (Case 11) also had bilateral cerebral infarcts, indicated by computed tomogra-

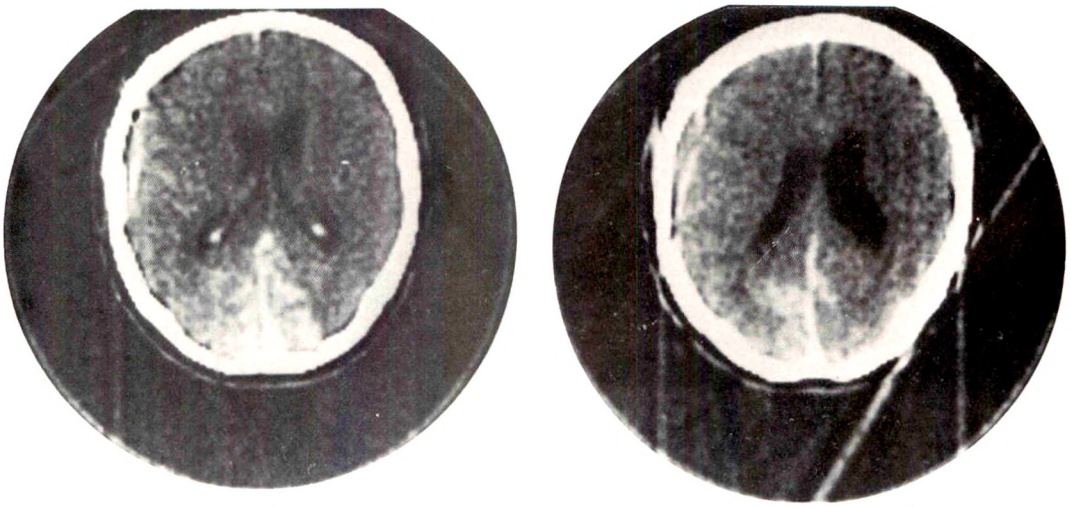


Fig.4 (Nepple, Appen, and Sackett). Case 7. Left, Computed tomography demonstrates bilateral occipital lobe radiodensity secondary to infarction. Right, computed tomography section 1 cm more cephalad than section in Figure 4, left, shows relatively normal right occipital lobe corresponding to the normal left homonymous inferior quadrant of vision.

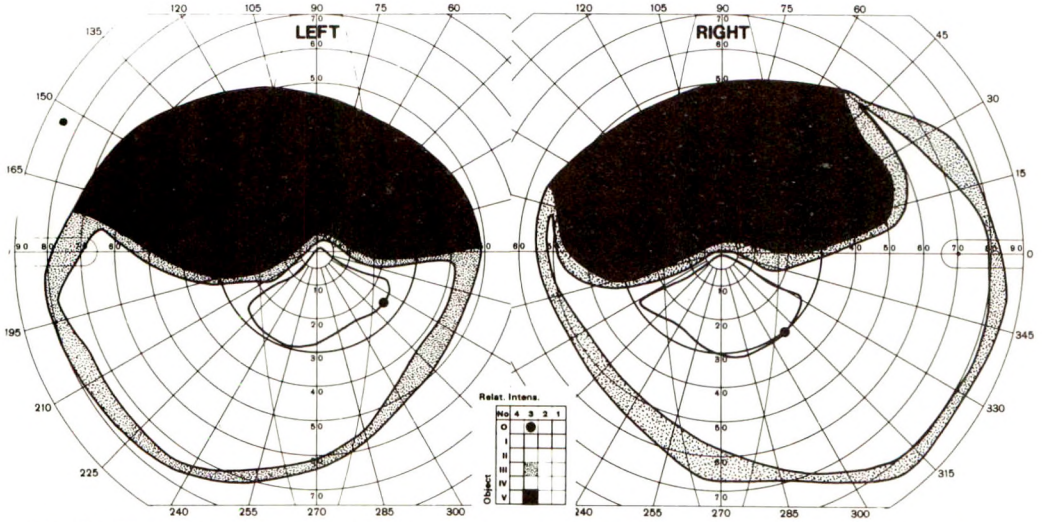


Fig. 5 (Nepple, Appen, and Sackett). Case 10. Visual field. Left homonymous superior quadrantanopia combined with a right homonymous superior quadrantanopia simulates an altitudinal visual field defect.

phy. He also retained good visual acuity despite extensive loss of visual field (Fig. 8).

Case 12 (Group 4)—A 54-year-old woman complained of poor vision bilaterally since an episode of anoxia from cardiac arrest during elective herniorrhaphy. Best corrected visual acuity was R.E.: 6/400 (3/200); L.E.: 6/600 (2/200). Intraocular pressures, pupils, fundi, optokinetic nystagmus, and electroretinogram were all normal. This patient was one of only three in the series who sustained loss of central vision (Fig. 9). The small vertical steps at the midline indicate the bilateral homonymous nature of the field defects.

Comment—The middle and posterior cerebral arteries perfuse adjacent regions of the brain. The boundary between the two areas is served by the distal branches of both vessels, which are under lowest pressure. This area is termed a watershed zone and may be infarcted when hypoten-

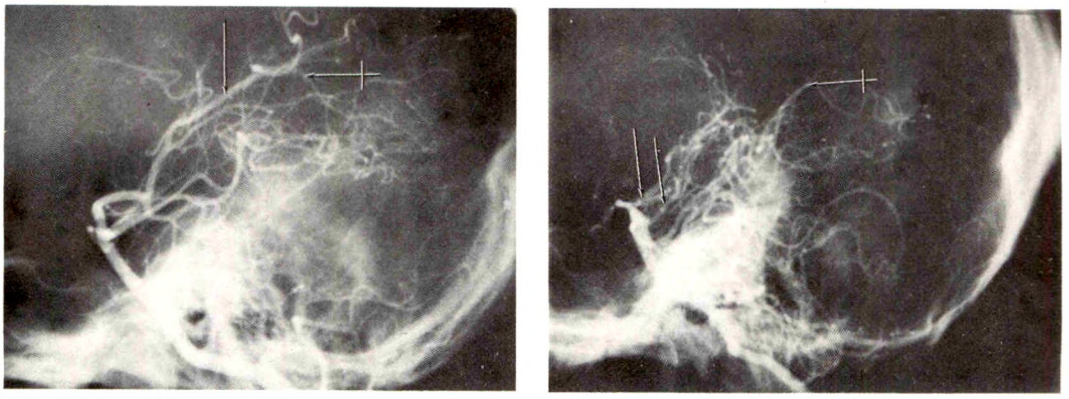


Fig. 6 (Nepple, Appen, and Sackett). Left, Normal lateral view of vertebral arteriography. Superior cerebellar artery (crossed arrow) serves as landmark indicating location of the tentorium. Arteries cephalad to that artery are supratentorial and are the parieto-occipital branches of the posterior cerebral arteries (arrow). Right, Case 10. Lateral view of vertebral anteriogram demonstrates nonfilling of the parieto-occipital branches of the posterior cerebral arteries above the tentorium. Proximal segments of posterior cerebral arteries are indicated by arrows, and the superior cerebellar artery by crossed arrow.

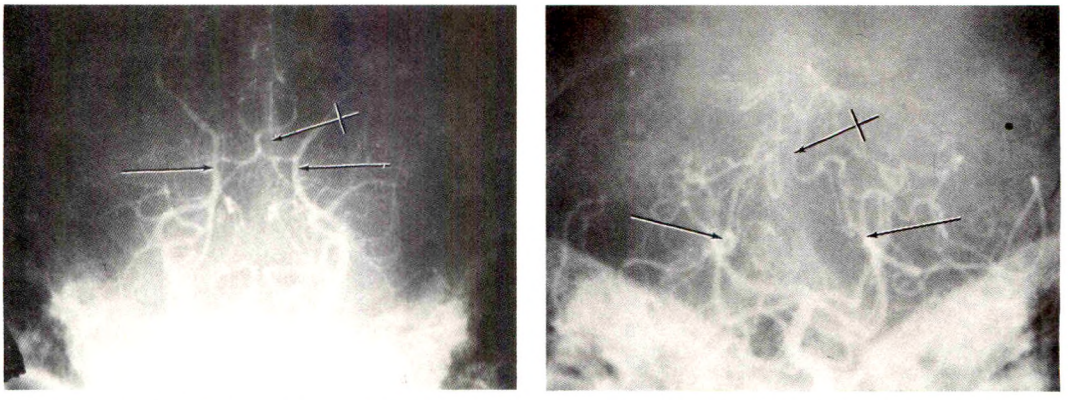


Fig. 7 (Nepple, Appen, and Sackett). Left, Frontal view of normal vertebral arteriography. Posterior cerebral arteries with parieto-occipital branches (arrows) are lateral to the superior cerebellar arteries (crossed (arrow). Right, Case 10. Frontal projection of vertebral arteriography shows nonfilling of parieto-occipital branches of the posterior cerebral arteries (arrows) above the level of the superior cerebellar arteries (crossed arrow).

sion affects both arteries, but is spared when there is occlusion of only one of them.[3,4,13] When cardiac arrest occurs, the pump failure causes greatest ischemia at the watershed zone and thereby accounts for the predominant loss of central visual field, as occurred in this patient. In contrast, embolic occlusion of a posterior cerebral artery spares the watershed zone because of its perfusion by the corresponding middle cerebral artery.

This patient was one of the remaining four whose diseases were caused by diverse factors. The patients with bilateral homonymous hemianopia secondary to progressive multifocal leukoencephalopathy (Case 14) and cardiac surgery (Case 13) have been previously described.[14,15] The other patient (Case 15) was a 45-year-old woman with a history suggestive of migraine. Following discovery of her bilateral homonymous hemianopia,

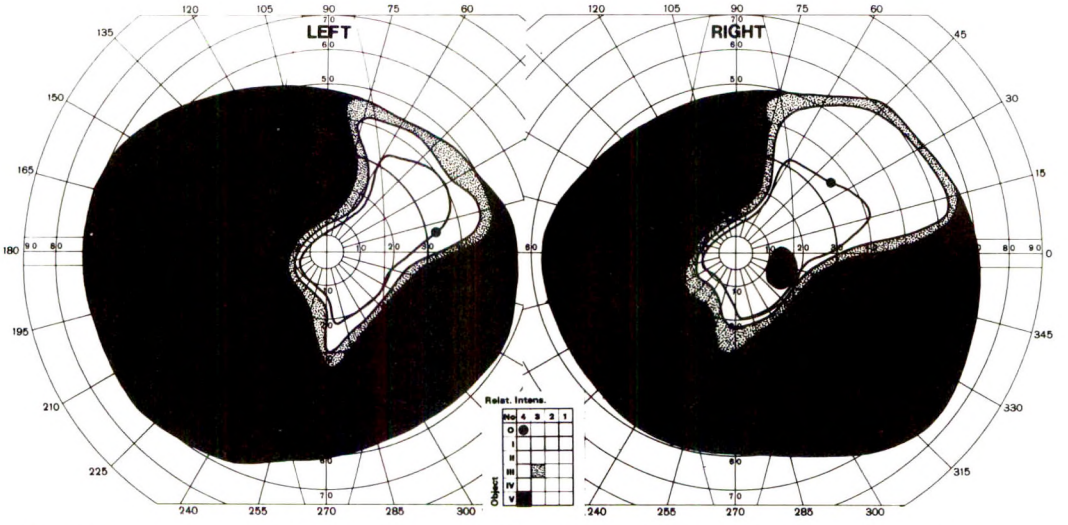


Fig. 8 (Nepple, Appen, and Sackett). Case 11. Visual field. Almost total left homonymous hemianopia combined with right homonymous inferior field loss.

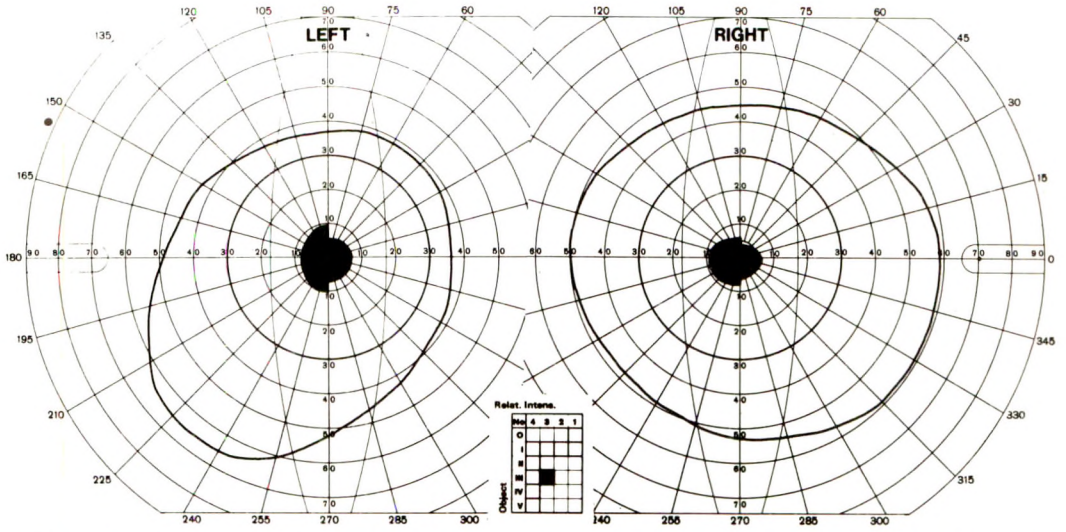


Fig. 9 (Nepple, Appen, and Sackett). Case 12. Visual field. Vertical steps indicate the bilateral homonymous character of the central visual field loss, slightly more extensive in the left homonymous field than in the right.

diagnostic studies revealed a type 4 hyperlipidemia, which resolved after discontinuation of oral contraceptives. Her angiogram documented severe bilateral posterior cerebral artery disease.

Results

The group studied consisted of ten men and five women ranging in age from 12 to 73 years (Table). Results of external, pupil, motility, and fundus examinations were normal in 11 patients. Visual acuity was generally equal in both eyes and was 6/7.5 (20/25) or better bilaterally in 11 of the 15 patients. One patient (Case 5) had visual acuity of R.E.: 6/6 (20/20), L.E.: 6/12 (20/40). The reason for the reduced visual acuity of the left eye remained uncertain. Three patients had visual acuity of 6/60 (20/200) or less. Optokinetic nystagmus was normal in all ten patients tested. Four patients had abnormal neuro-ophthalmic findings other than the visual fields. Of two patients with ocular motility abnormalities, one man (Case 6) had internuclear ophthalmoplegia, skew deviation, and nystagmus. The other (Case 11) had a right sixth nerve paresis, skew deviation, and a right Horner's syndrome. In one patient (Case 4) ophthalmoscopic examination revealed two cholesterol crystals. A positive Marcus Gunn pupil sign that was difficult to explain was present in one patient (Case 5).

In all patients the medical history was important in clarifying the cause of the bilateral homonymous hemianopia. For nine patients, a definitive neurologic diagnosis was established by techniques other than neuro-ophthalmic examination, including cerebral angiography (three patients); computed tomography (three patients); technetium Tc 99m brain scan (one patient); and autopsy (two patients). Another patient (Case 6) had a computed tomography scan that confirmed infarction of the right occipital lobe, but visual fields showed a definite right homonymous defect in addition to the total left homonymous hemianopia. Bilateral cortical occipital lesions were diagnosed clinically in the six remaining patients.

TABLE

BILATERAL HOMONYMOUS HEMIANOPIA

Case No.	Age (yrs)	Sex	Visual Acuity*	Bilateral Homonymous Hemianopia At First Examination†	Other Neuro-Ophthalmic Abnormalities	Positive Diagnostic Studies	Etiology
1	73	M	6/6 (20/20)	–	–	Autopsy	ASVD‡
2	64	M	6/6 (20/20)	+	–	CT§ Scan	ASVD
3	49	F	6/4.5 (20/15)	–	–	None	ASVD
4	64	M	6/6 (20/20)	+	+	None	ASVD
5	60	F	R.E.:6/6 (20/20) L.E.:6/12 (20/40)	–	+	Angiography	ASVD
6	50	M	6/7.5 (20/25)	+	+	CT Scan	ASVD
7	48	M	6/6 (20/20)	+	–	CT Scan	Tentorial herniation
8	12	M	6/6 (20/20)	+	–	None	Tentorial herniation
9	44	M	6/6 (20/20)	+	–	None	Tentorial herniation
10	27	F	6/4.5 (20/15)	–	–	Angiography	Migraine
11	37	M	6/6 (20/20)	–	+	CT Scan	Migraine
12	54	F	6/400 (3/200)	+	–	None	Cardiac arrest
13	48	M	6/60 (20/200)	+	–	Brain scan	Cardiac surgery
14	63	M	6/60 (20/200)	+	–	Autopsy	PML‖
15	45	F	6/6 (20/20)	+	–	Angiography	Idiopathic¶

* Corrected and equal in both eyes except in Case 5.
† + designates present; –, absent.
‡ ASVD designates arteriosclerotic vascular disease.
§ CT designates computed tomography.
‖ PML designates progressive multifocal leukoencephalopathy.
¶ The patient was taking an oral anovulatory agent at the time of onset of bilateral homonymous hemianopia.

DISCUSSION

Forster[16] first described a patient with a well-documented partial bilateral homonymous hemianopia in 1890. The 49-year-old patient sustained a right, followed by a left homonymous hemianopia with sparing of central vision. Recent ophthalmic papers in English have not emphasized this condition. Previous ophthalmic reports[6,17] and neurologic studies[3,4] have not presented documentation of the visual field abnormalities by means of modern techniques. The characteristics of the ophthalmologic examination that should suggest this diagnosis include (1) similarly shaped visual field defects on corresponding sides of the vertical midline for each eye; (2) equal visual acuity for each eye, which generally is normal (as in 75% [12 of 15] of our patients); (3) normal pupils and fundi; (4) ocular motility that is generally normal unless there are coexisting brain stem lesions.

The cerebral lesions almost invariably result from cerebrovascular insufficiency,

most commonly caused by arteriosclerosis, tentorial herniation from increased intracranial pressure, and migraine. The cerebral lesions are generally in the occipital lobes, and the posterior cerebral arteries are the vessels most commonly affected. Brain tumor did not occur in our series, and no bilateral homonymous hemianopia occurred in 849 patients with visual field defects and brain tumors studied by Tönnis as reported by Schäublin.[4]

Contrary to prior reports, the occurrence of this visual abnormality is not rare. The ophthalmologist must consider this diagnosis in the examination of any patient with bilateral visual deficits that are not accounted for by visible ocular abnormalities.

SUMMARY

Bilateral homonymous hemianopia occurred in 15 patients seen during a four-year period. Persons with this visual deficit had similarly shaped visual field defects on corresponding sides of the vertical midline for each eye, equal visual acuity which is generally normal, and normal pupil and fundus examinations. The most common causes of the bilateral posterior cerebral artery insufficiency were arteriosclerosis (40%), uncal herniation (20%), and migraine (13%).

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OPTIC NEURITIS COMPLICATING MEASLES, MUMPS, AND RUBELLA VACCINATION

EDWARD L. KAZARIAN, M.D.
Miami, Florida
AND
WALTER E. GAGER, M.D.
Milwaukee, Wisconsin

Optic neuritis complicating measles, mumps, and rubella vaccination has not been previously described, although monovalent measles and rubella administration are associated with systemic and neurologic abnormalities.[1-20] We describe herein a patient with bilateral optic neuritis following trivalent measles, mumps, and rubella vaccination. The purpose of this paper is to alert the ophthalmic community to this possible relationship. Vaccination programs will continue to expand and ultimately include most of the preschool population. Awareness of this relationship will alert us to the diagnostic possibility and its future documentation.

CASE REPORT

A 6-year-old boy was examined on Oct. 13, 1975, for bilateral optic disk swelling and decreased visual acuity. Three weeks before referral (Sept. 24, 1975) he had a routine physical examination and received a trivalent measles, mumps, and rubella vaccination. Eleven days after vaccination (Oct. 4, 1975) the child developed an oral temperature of 39.4° C, which lasted for one day. The child was otherwise well until Oct. 12, 1975, when he developed general malaise, left orbital pain on horizontal gaze, and inability to see with his left eye.

His medical and surgical history were unremarkable. There was no family history of multiple sclerosis, Leber's optic neuritis, or other ocular or central nervous system disease. The boy had no known allergies and was not taking medication.

Physical examination on admission was unremarkable except for the ocular findings. Visual acuity was R.E.: 6/7.5 (20/25); L.E.: finger counting at one foot. The left pupil had an afferent defect. The right optic disk was elevated, and spontaneous venous pulsations were present (Fig. 1). In the left fundus there were elevation of the optic disk, congestion of the nerve fiber layer, scattered splinter hemorrhages, and no spontaneous venous pulsations (Fig. 2). Quantitative visual field testing on the Goldmann perimeter with V_{-4e} and the I_{-4e} targets was normal on the right eye and not obtainable on the left eye because of poor fixation. Extraocular muscle function, anterior segment, the vitreous, the macula, and the peripheral retina were all normal for each eye.

Studies included computed axial tomography of the brain, which was normal. A routine skull x-ray film series, coned down views of the sella, orbital apices, sinuses, and optic foramina were also normal. The diagnosis of bilateral optic neuritis complicating the vaccination was made. Complete blood cell count, serum chemistry, serum protein electrophoresis, fluorescent treponemal antibody test, viral serology, and urinalysis were normal. Cerebro spinal fluid analysis revealed glucose, 88 mg/100 ml; protein, 11.6 mg/100 ml; and chloride, 119 mg/100



Fig. 1 (Kazarian and Gager). Optic disk of right eye 21 days after vaccination.

From the Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Florida (Dr. Kazarian) and the Eye Institute, Medical College of Wisconsin, Milwaukee, Wisconsin (Dr. Gager). This study was supported in part by Institutional National Research Service Award EY-07021 from the National Institutes of Health (Dr. Kazarian).

Reprint requests to E. L. Kazarian, M.D., 24 Wheeler Rd., North Grafton, MA 01536.

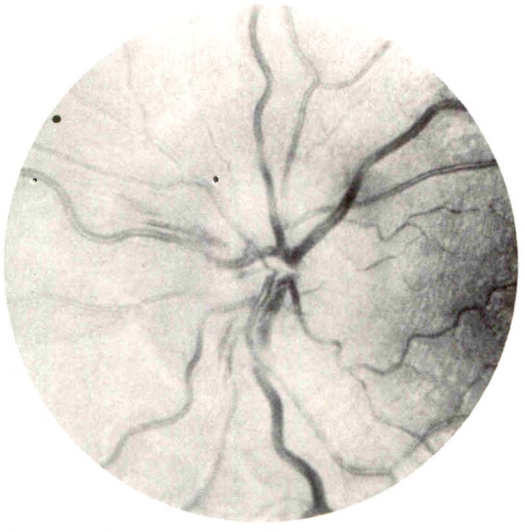


Fig. 2 (Kazarian and Gager). Optic disk of left eye 21 days after vaccination.



Fig. 3 (Kazarian and Gager). Optic disk of right eye 14 months after vaccination.

ml. The spinal tap was traumatic with many red blood cells present. No inflammatory cells were reported, and cultures of this fluid were negative for pathogens.

The patient was given 40 mg of prednisone orally each day. Five days later, the visual acuity improved to R.E.: 6/6 (20/20); L.E.: 6/120 (20/400). The visual acuity in the left eye continued to improve and was 6/21 (20/70) on the tenth day. Spontaneous venous pulsations were present bilaterally at that time.

After ten days, the dosage of oral prednisone was gradually reduced during the ensuing several weeks. The visual acuity returned to 6/6 (20/20) in each eye within several weeks, but the afferent conduction defect persisted on the left. Visual fields remained normal on the right, but showed a persistent, irregular, inferior defect on the left. The patient's condition has remained stable for 14 months (Figs. 3 and 4).

Discussion

The attenuated live virus vaccination programs against measles, mumps, and rubella have been highly effective. A high percentage of patients have demonstrated an excellent immune response with monovalent[21–30] or trivalent[21,25,26,31] vaccine administration. Vaccination has also been safe.[1,3,6–10,13,17,21–23,28–32]

Mumps vaccination causes no discernible clinical reaction in children.[21,23,31] This compares favorably with the incidence and severity of encephalitis, optic neuritis, and other central nervous system involvement reported with natural mumps infection.[22,33–36]

Rubella vaccination has been followed by significant systemic and neurologic complications. Children rarely develop symptoms, but adult women frequently report arthralgias.[4–9,14–20,31] Thrombocy-

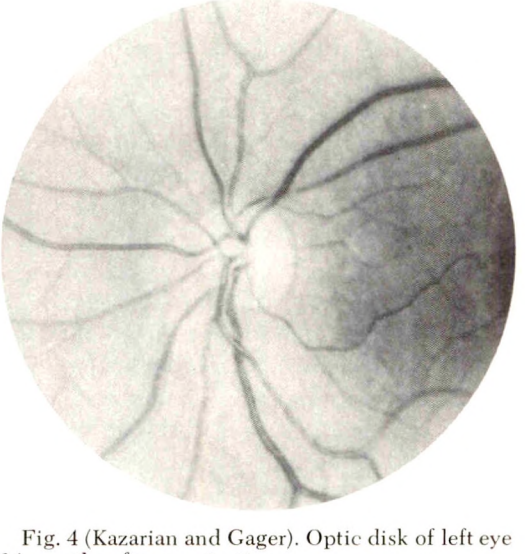


Fig. 4 (Kazarian and Gager). Optic disk of left eye 14 months after vaccination.

topenic purpura, ataxia, aseptic meningitis, transverse myelitis,[4,5] and polyneuritis[10,11] have developed following rubella vaccination. The complications were definitely fewer than the 1:5,000 incidence of encephalitis with natural rubella infection.[36]

Measles vaccination is also associated with complications. Eighty-four cases of neurologic disorders following measles vaccination were reported to the Communicable Disease Center in Atlanta, Georgia, from 1963 to 1974.[3] Fifty-nine of the cases occurred within 30 days of the vaccination date, and 54 cases (76%) occurred between six and 15 days after the vaccination. No etiologic factor except for the vaccination could explain the severe neurologic involvement in the 59 patients. The clustering of 76% of these cases in a period of six to 15 days after vaccination was thought to be highly significant in relating the vaccine administration to the complication. The complications included encephalitis,[1] encephalomyelitis, chorea, meningitis, transverse myelitis,[3] cranial nerve palsies,[2,3] and cerebellar ataxia.[12] The incidence of neurologic complications was 1.6:1 million vaccinations.[3] This is less than the 1:1,000 cases of encephalitis that occurred following natural measles infection.[3,36]

The remarkable tendency for these complications to occur from one to three weeks following vaccination is highly suggestive of a relationship between the vaccination and the complication. The time between six and 15 days is the expected incubation period for maximal virus replication and the onset of viremia.[4] Our patient had the clinical symptoms of optic neuritis associated with visual loss 18 days after vaccination. The timing of the patient's symptom complex is close to the known incubation period of the natural virus, and it coincides well with the onset of the other postvaccination neurologic complications noted above. This is highly suggestive of a causal relationship between the vaccination and the optic neuritis.

To the best of our knowledge, optic neuritis following trivalent measles, mumps, and rubella vaccination has neither been described nor reported to the Center for Disease Control in Atlanta, Georgia (N. A. Halsey, M.D., personal communication, Dec. 15, 1977).

Summary

A 6-year-old boy developed bilateral optic neuritis with decreasing visual acuity 18 days after administration of live attenuated trivalent measles, mumps, and rubella vaccine. The patient was treated with oral corticosteroids. The optic neuritis resolved within several weeks and normal vision returned. An afferent pupillary defect persisted in the more severely involved eye for 14 months following vaccination.

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RETINITIS SECONDARY TO ACQUIRED SYSTEMIC TOXOPLASMOSIS WITH ISOLATION OF THE PARASITE

JOSEPH B. MICHELSON, M.D., JERRY A. SHIELDS, M.D., P. ROBB MCDONALD, M.D., MICHAEL A. MANKO, M.D., ANDREAS A. ABRAHAM, M.D., AND JAY L. FEDERMAN, M.D.

Philadelphia, Pennsylvania

The histology of ocular toxoplasmosis has been accurately defined as a retinochoroiditis, with the organism located in the necrotic retina and not in the inflamed choroid.[1] Isolation of the organism from the eye is rarely possible, except from an enucleated eye,[2,3] aspirated aqueous,[4] or subretinal fluid.[5] In systemic toxoplasmosis, the diagnosis depends on the demonstration of the organism, a positive serologic reaction, or both. The concomitant systemic and ocular involvement of toxoplasmosis infection is rare and occurs in only 1% of cases of systemic toxoplasmosis, most of which are lymphadenopathic.[4]

We describe herein a case of systemic toxoplasmosis of the febrile lymphadenitis type, in which a retinitis followed a heterophile-negative infectious mononucleosis syndrome for which there was no apparent cause. Organisms consistent with toxoplasmosis were identified from an axillary node biopsy, and the diagnosis was confirmed by isolation of the toxoplasma organisms after intraperitoneal inoculation in laboratory mice.[6,7] This case is unusual because the diagnosis was unsuspected until the retinitis occurred, which suggests systemic toxoplasmosis as the underlying cause.

From the Retina Service, Wills Eye Hospital and Research Institute (Drs. Michelson, Shields, McDonald, and Federman), and the Research and Medical Departments, Lankenau Hospital (Drs. McDonald, Manko, Abraham, and Federman), Philadelphia, Pennsylvania. This work was supported in part by the Retina Research and Development Foundation, Philadelphia, and the Lions Club of Pennsylvania. Dr. Michelson was a Heed Foundation Fellow (1977-1978).

Reprint requests to Jay L. Federman, M.D., Retina Service, Wills Eye Hospital, 1601 Spring Garden St., Philadelphia, PA 19130.

CASE REPORT

A 43-year-old woman first noticed the onset of malaise while visiting a mink farm in northeastern Pennsylvania. During the next 11 days she noted a sore throat, night sweats, progressive malaise, and spiking temperature increases to 39.6° C daily. She was then hospitalized, and the physical examination revealed a temperature that ranged from 37.9° C to 39.6° with nontender cervical lymphadenopathy. Hepatosplenomegaly was not noted at this time.

Laboratory data revealed mildly increased serum glutamic oxalotransaminase and lactate dehydrogenase levels. The serum albumin was slightly decreased. The sedimentation rate was 22 mm/hr. The white blood cell count was 5,700 cells/mm^3 with 53% neutrophils and 41% lymphocytes. Some of the lymphocytes were atypical. Blood cultures, Australia antigen, febrile agglutinins, urinalysis, stool culture, and throat culture were all negative. Numerous x-ray film studies were also negative. The liver enzyme abnormalities returned to normal, fever resolved, and the patient was discharged after seven days of hospitalization with the diagnosis of possible heterophile-negative infectious mononucleosis.

The day after discharge from the hospital, the patient noted the sudden appearance of a "spot" in her right visual field. Three days later, one of us (P.R.M.) noted a white retinal lesion superior to the fovea (Fig. 1). Slit-lamp examination revealed a 1+ aqueous flare and cell in both eyes. The patient was then admitted to the hospital for further examination and treatment with a diagnosis of acute systemic toxoplasmosis. Fluorescein angiography after admission revealed inflammatory involvement of the retinal layers only (Fig. 2). Physical findings at this time included cervical lymphadenopathy, 2 × 3-cm nontender bilateral axillary lymph nodes, and hepatosplenomegaly. The patient was afebrile.

Laboratory data revealed a white blood cell count of 5,300 mm^3 with 47% neutrophils and 39% lymphocytes. A few of the lymphocytes were atypical. The Monospot test was negative. The serum glutamic oxalotransaminase level had increased to 80 units. The initial indirect fluorescent antibody test for toxoplasmosis was 1:1024, and five days later it was 1:2048.

Two days after admission, an excisional biopsy of one of the axillary lymph nodes was done. Acid-fast



Fig. 1 (Michelson and associates). A white retinal infiltrate is just superior to the fovea in the right eye.

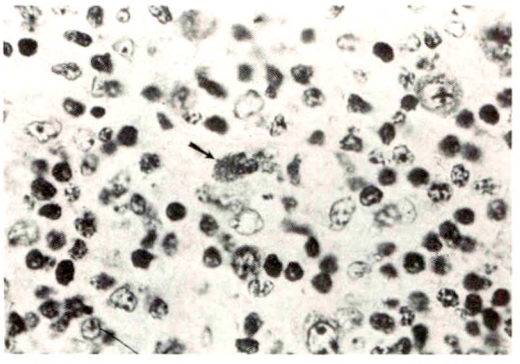


Fig. 3 (Michelson and associates). Section of lymph node biopsy demonstrating marked histiocytic hyperplasia with cysts of *Toxoplasma gondii* organisms (arrow, Giemsa stain, ×250).

and fungal stains of the tissue were negative. The lymph node biopsy showed marked histiocytic hyperplasia, consistent with toxoplasmosis; on Giemsa stained slides, structures consistent with *Toxoplasma gondii* cysts were seen (Fig. 3). A portion of the lymph node was macerated, and a suspension of the material was injected intraperitoneally into purebred toxoplasma-free mice. Several animals were injected with saline intraperitoneally to serve as controls. Several days later, the test animals, as well as the appropriate controls, were killed and trophozoites of *T. gondii* were isolated from the test animals (Fig. 4).

At admission, the patient began receiving intramuscular adrenocorticotropic hormone for several days and 20 mg of prednisone daily for two weeks. Subsequently, the dosage was changed to 40 mg every other day. The prednisone was gradually reduced during the next eight weeks. Therapy was also begun with 4 g of sulfadiazine daily, 25 mg of

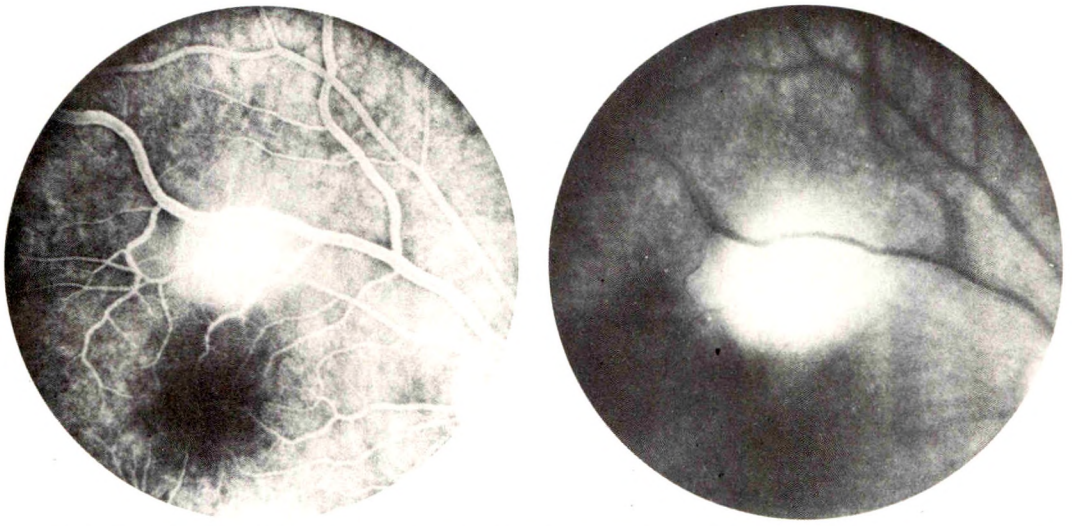


Fig. 2 (Michelson and associates). Left, Fluorescein angiography during early filling phases reveals leakage from retinal vessels, causing a fluffy hyperfluorescence of retinal tissue. Right, A more intense hyperfluorescence corresponding to late staining of the retinal inflammatory lesion.

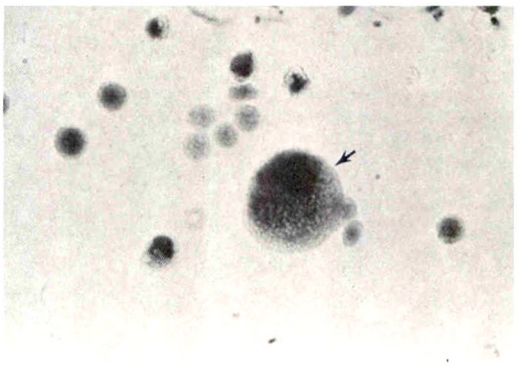


Fig. 4 (Michelson and associates). Smear from mouse peritoneal exudate showing toxoplasma cyst and organisms (arrow) (Giemsa stain, ×250).

pyrimethamine twice a day, 3 mg of folinic acid intramuscularly every other day, and atropine 1% ophthalmic drops. Because the platelet count decreased significantly, the sulfadiazine and pyrimethamine were discontinued for several days, then reinstituted at the lower dose of 2 g daily and 25 mg daily, respectively. Administration of all medications was stopped at the tenth week after the second hospitalization.

Repeat color photographs and fluorescein were taken one week later, and the retinitis appeared more intense. Fundus photographs (Fig. 5) and fluorescein angiograms (Fig. 6) taken three months later showed the lesion to be much smaller, with traction demonstrated from the resolving lesion into the macular area. Visual acuity was 6/9 (20/30) at this time with no scotoma noted on Amsler grid testing. Both fluorescein studies showed focal involvement of the retina, with minimal or no involvement of the retinal pigment epithelium or choroid.

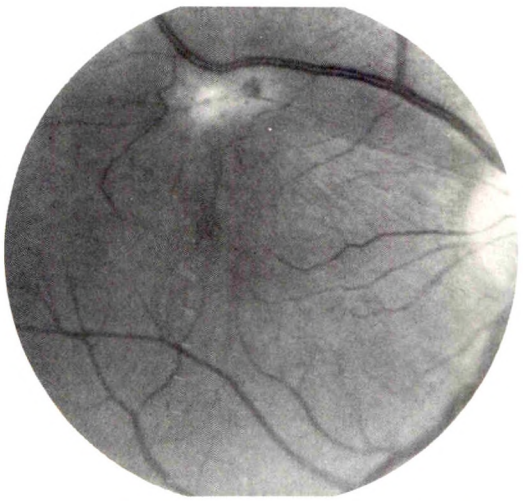


Fig. 5 (Michelson and associates). The white retinal infiltrate appears smaller, with traction lines radiating from macular area.

Discussion

Ocular toxoplasmosis is probably the most important cause of posterior uveitis in man.[8] It may occur either as a congenital form or as an acquired infection. Ocular involvement is common in congenital toxoplasmosis, but its recognition is rare in acquired systemic toxoplasmosis.[9] Although our case strongly suggests acquired toxoplasmic retinitis, the less likely possibility of a reactivation of subclinical congenital toxoplasmosis cannot be unequivocally excluded.

The acquired systemic toxoplasma infection may have a varied clinical expression. It may manifest itself as an exanthematous skin rash, resembling a rickettsial infection. Ocular involvement has not been documented with this rare form of the disease. It may occur as an influenza-type syndrome, characterized by malaise, fever, headache, and muscle pains. Central nervous system involvement may manifest itself as meningitis or encephalitis, and patients with this affliction have the highest incidence of ocular involvement (19%).[10] The most common manifestation of systemic toxoplasma involvement is the lymphadenopathic type, as described in this case, but ocular involvement is considerably less common in this form of the disease than it is for the meningoencephalitic form.

Retinitis is associated with 1% of the patients with the lymphadenopathic type of systemic disease.[2] The febrile lymphadenitis form, as in our case, may run a course that resembles the syndrome of infectious mononucleosis, with chills, fever, malaise, headache, and localized or generalized lymphadenitis. Either an in-

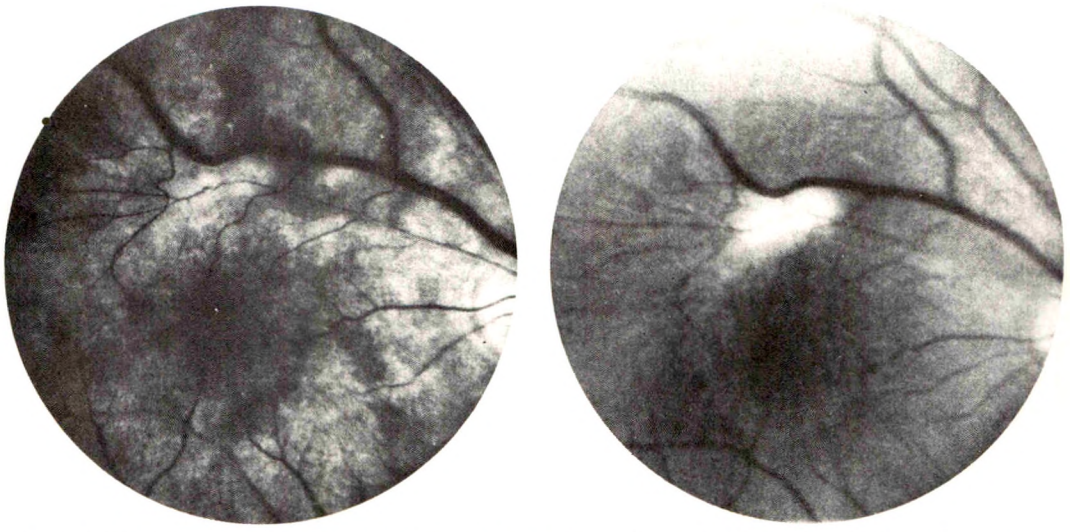


Fig. 6 (Michelson and associates). Left, Fluorescein angiography during choroidal filling shows essentially no transmission, demonstrating little or no pigment epithelial involvement. Right, Hyperfluorescence is seen during the late phases of the study because of minimal leakage from the retinal arteriole and staining of the intraretinal tissue.

creased antibody titer[11] or a seroconversion[12] makes the serologic diagnosis possible. Toxoplasma may be isolated from the affected lymph nodes, especially those of the posterior cervical chain.[13] The affected node should be minced and injected intraperitoneally into laboratory mice whose lack of prior infection is determined.[6,7,9] Although viable organisms may be isolated from lymph node tissue,[6,7,9,10,13] this is not necessarily indicative of acute infection. Viable organisms can remain dormant in cysts of once infected hosts throughout the lifetime of the host.[14]

In our case a middle-aged woman developed a heterophile-negative infectious mononucleosis syndrome, which would have gone undiagnosed had she not subsequently developed a retinitis that suggested the diagnosis of toxoplasmosis. This patient is unusual because hers was one of the few cases of toxoplasmosis in which the organisms were isolated in association with an acute retinitis.

Summary

A 43-year-old woman developed a heterophile-negative infectious mononucleosis syndrome for which no cause was apparent. During her illness she developed subjective changes in the central vision of her right eye and had focal retinal inflammation, which suggested the diagnosis of toxoplasmosis. The clinical course was accompanied by an increased titer to *Toxoplasma gondii*. Organisms were isolated from lymph node tissue and injected into the peritoneum of mice from which organisms were harvested.

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OPHTHALMIC MINIATURE

My boats, the usual small dug-out for myself and the larger one for kit and servants, drew up opposite the company's compound. The Forest Manager saw me down to the bank.

"Want to see me sneeze?" he queried suddenly.

What does a junior forest assistant say to his boss when asked such a question? Since I was his junior, I replied in the affirmative, whereupon he glanced quickly up at the cloudless heavens and then let forth a sternutation that sent the ready plover up in clouds above the trees on the opposite bank.

"I can always sneeze when I look at the sun," he said with satisfaction.

Reginald Campbell, *Teak Wallah*
London, Hodder & Stoughton, 1935.

EARLY DIAGNOSIS AND EVOLUTION OF DOMINANT RETINITIS PIGMENTOSA

NORMAN S. LEVY, M.D.

Lake City, Florida

The electroretinographic response to light stimulation has been widely used to evaluate and document the presence of retinitis pigmentosa. Several investigators have used the electroretinogram (ERG) in offspring and younger siblings of patients with retinitis pigmentosa to establish the diagnosis and to determine the visual prognosis in the affected individuals.[1-4]

Bjork and Karpe[1] described a 7-month-old child with an extinguished ERG and a family history of dominant retinitis pigmentosa, who developed evident clinical disease by 3 years of age. Subnormal electroretinographic responses have also been documented at 3 years of age in a member of another family with dominant retinitis pigmentosa.[2] We describe herein the earliest ERG abnormalities in autosomal dominant retinitis pigmentosa measured initially at 5 months of age and followed serially thereafter, in a child who later developed clinical evidence of the disease. We were able to document electroretinographically its early onset and follow the progression of this variety of retinitis pigmentosa.

MATERIAL AND METHODS

All studies within the first two years of life were performed with a contact lens electrode overlying a soft contact lens. Pupils were dilated with 10% phenylephrine and 1% cyclopentolate. Anesthesia was obtained with intramuscular ketamine hydrochloride. The patient was dark-adapted for 12 minutes.

Stimulation was provided by a ganzfeld system. The white light flash from the Grass photostimulator lasted 10 μsec. The interval between paired flashes varied from one second to 75 msec.[5-10] Light intensity was controlled with neutral density filters and ranged from 1.8 to 3.7 log trolands. Only white light was used throughout this study. The signals were summated and averaged by computer and displayed on an oscilloscope before recording.

The ERG record at 4 years of age reflected the response to a single white flash stimulus. Computer averaging was not performed.

CASE REPORT

The proposita, a 5-month-old girl (Fig. 1) had been the product of a normal gestation and delivery without complications. Her pediatrician, aware of the hereditary nature of retinitis pigmentosa and a family history of this disease, referred her for examination to assess the presence of the disease at an early age.

The proposita had bilateral fixation and appeared orthophoric. The pupils responded to light. The

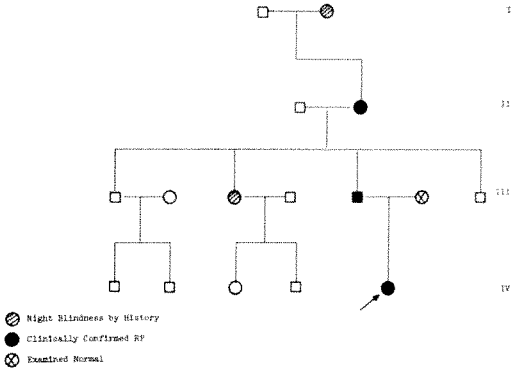


Fig. 1 (Levy). The paternal family tree indicates four generations of retinitis pigmentosa. The proposita is noted by the arrow. Her father and grandmother were documented as having retinitis pigmentosa.

From the Florida Ophthalmic Institute and the Veterans Administration Hospital, Lake City, Florida.

Reprint requests to Norman S. Levy, M.D., Chief, Ophthalmology Section, Veterans Administration Hospital, Lake City, FL 32055.

anterior segments, lens, vitreous, retina, and disk all appeared to be normal. There was a subalbinotic appearance to the retina, but no pigment clumping or any attenuation of the vessels.

Under ketamine anesthesia, a computer-averaged electroretinographic response was obtained when the patient was 5 months old. The light-adapted (cone) response was normal. However, following dark adaptation, the b-wave amplitude was well below our normal mean of 150 to 300 mV for that age (Fig. 2). Additionally, pronounced X-waves were present in the dark-adapted response. Following dark adaptation, paired light stimuli at intervals as short as 75 msec did not demonstrate the usual suppression of the second b-wave response (Fig. 3).

When the patient was 8 months old, the ERGs were repeated. Reduction in the amplitude of the dark-adapted b-wave was confirmed (Fig. 2). After paired stimuli, no appreciable suppression of the second b-wave was present (Fig. 3). A normal light-adapted (cone) ERG persisted. When the patient was 10 months old, a reduction from previous measurements in the dark-adapted b-wave amplitude was clearly apparent (Fig. 2).

Single-flash electroretinograph recordings, obtained when the patient was 4 years old, revealed an extinguished scotopic b-wave and tiny to absent a-waves (Fig. 2). The photopic flicker response at 30 Hz was normal.

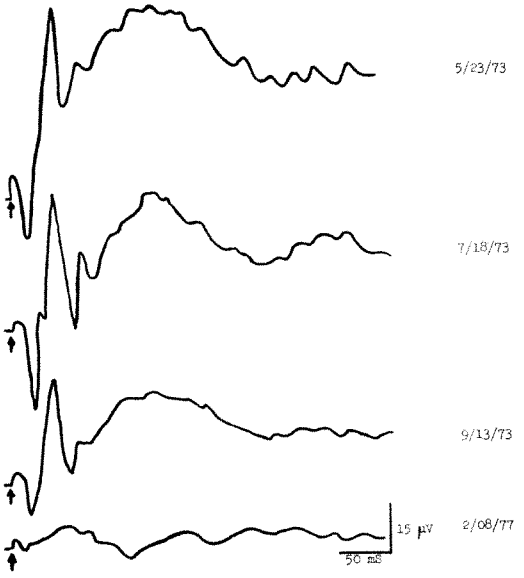


Fig. 2 (Levy). Electroretinographic tracings after dark adaptation, obtained serially over the first four years. Stimulus intensity was 2.8 log trolands, with a white light from a Grass photostimulator. The earliest tracing was recorded when the patient was 5 months old. The amplitude of the b-wave is approximately 90 mV, well below the normal mean for this stimulus intensity. A reduction in the b-wave amplitude progresses during the testing period. Photopic responses were normal during this same period. No subjective visual function abnormalities were found.

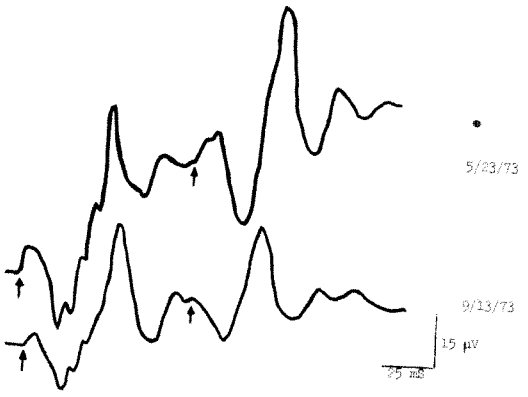


Fig. 3 (Levy). The dark-adapted electroretinographic response to paired light stimuli at an interval of 75 msec. The second response is almost as large as the initial response when the patient was 5 months and 8 months old. This contrasts markedly with the usual suppression of the second b-wave response after a stimulus pair of 75-msec interval.

When the patient was 4 years old, no abnormality had been documented in her subjective visual function. Visual acuity was R.E.: 6/9 (20/30), L.E.: 6/6 (20/20), and fields were full to confrontation. Objectively, some fine pigment clumping could be noted in the periphery, and attentuation of vessels had become apparent centrally (Fig. 4).

The father of the proposita (Fig. 1) had documented retinitis pigmentosa, which was functionally apparent by age 15 years and had constricted his visual fields to less than two degrees by age 23 years. The fundus findings were characteristic of retinitis pigmentosa, including arteriolar attentuation, bull's eye macula, disk pallor, and peripheral pigment spicules. The scotopic ERG was extinguished. The dark adaptation was clearly abnormal with a fall of only one log unit during a 30-minute period and a delay in the rod-cone breakpoint to five minutes. The electro-oculogram was also markedly abnormal. Color vision was intact on the Farnsworth-Munsell 100 hue test. The mother of the proposita showed no functional or ophthalmoscopic abnormality. Her scotopic ERG, paired scotopic ERG (Fig. 5), dark adaptation, and color vision were all normal.

A paternal grandmother was 56 years old when first seen (Fig. 1). By age 32, she had decreasing visual acuity caused by retinitis pigmentosa. Visual acuity had decreased to light perception bilaterally without color perception at age 56 years. Additionally, she demonstrated anterior and posterior subcapsular and nuclear lens changes. Her fundi were visible with difficulty on the right and revealed a pale disk, large pigment clumps, and a few narrowed arteries.

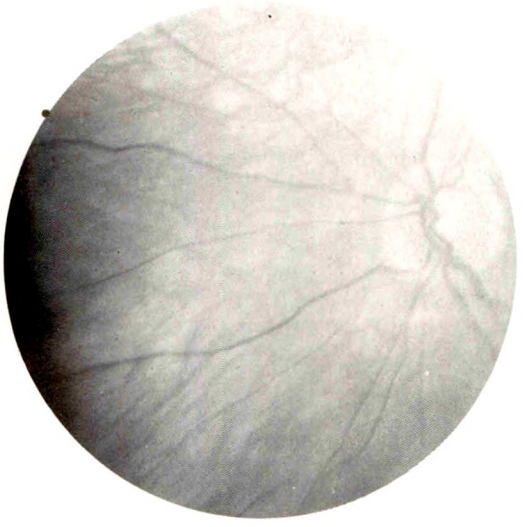


Fig. 4 (Levy). Ophthalmoscopic photograph of patient at 4 years of age. Note minimal arteriolar attenuation. There was fine peripheral clumping, but no other ophthalmoscopic abnormalities.

Discussion

The early diagnosis of retinitis pigmentosa in young members of families in which this disease has been documented can be made electroretinographically.[1-4]

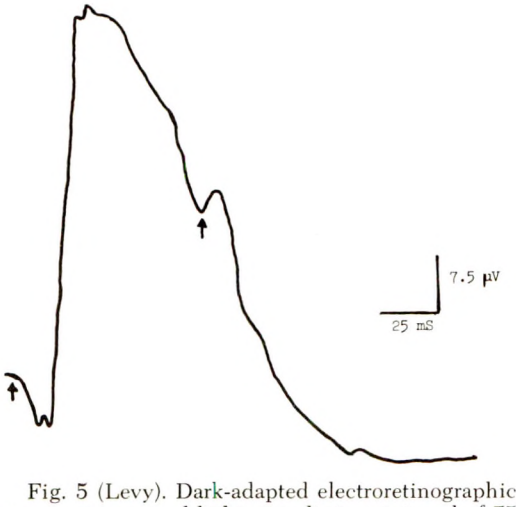


Fig. 5 (Levy). Dark-adapted electroretinographic response to paired light stimuli at an interval of 75 msec in the mother of the proposita. Note the almost total suppression of the second b-wave response (arrow).

The earliest abnormalities noted in retinitis pigmentosa included reduced scotopic b-wave amplitude and delayed latency.[11,12] Cone function is normal. We had the opportunity to examine our patient at an earlier age than those patients described in previous reports.

The electrophysiologic abnormalities of retinitis pigmentosa of the autosomal dominant variety were found when the patient was 5 months old. In one member of a family with this form of the disease, the electrophysiologic progression occurred rapidly during the first year, although no ophthalmoscopic changes were present.

The early dark-adapted electroretinographic abnormalities noted in our patient consisted of a progressive reduction in the b-wave amplitude to single flashes as well as the presence of a prominent X-wave. A more sensitive measurement was the absence of postflash suppression of the second b-wave of closely paired responses.

Documentation of these electrophysiologic abnormalities suggests that the functional defect in retinitis pigmentosa may be present early in life. In our case of autosomal dominant retinitis pigmentosa, the normally seen postflash b-wave suppression seems to be absent. Previously, this had not been noted and is a useful measurement that may have important implications in an understanding of the disease process.

Studies in an animal model of retinitis pigmentosa by Edwards and Szamier[13] indicate that in cultured RCS rat pigment epithelial cells, a specific defect in the mechanism for phagocytizing outer segments exists. The absence of postflash ERG suppression, which we have demonstrated in the earliest stages of the human disease process, should be assessed in the animal model to determine the model's electroretinographic similarity to human retinitis pigmentosa.

SUMMARY

A 5-month-old girl with retinitis pigmentosa was the healthy offspring of a family with progressive autosomal dominant retinitis pigmentosa. Serial evaluation by both electroretinograph and ophthalmoscopy over a four-year period confirmed the diagnosis and indicated that as early as 5 months of age, electroretinographic abnormalities were present in the patient. These consisted of a reduction in the dark-adapted b-wave amplitude, prominent X-wave, and no suppression of the second b-wave response to paired light stimuli at 75 msec. Progressive reduction in the scotopic electroretinograph amplitude has occurred over the ensuing four years, although light-adapted (cone) function still appears normal. Clinical evidence of retinitis pigmentosa became apparent only late in the patient's third year when fine peripheral pigment clumping and vessel attentuation could be seen.

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REAPPRAISAL OF CALLENDER'S SPINDLE A TYPE OF MALIGNANT MELANOMA OF CHOROID AND CILIARY BODY

IAN W. MCLEAN, M.D., LORENZ E. ZIMMERMAN, M.D., AND RICHARD M. EVANS, M.D.

Washington, D.C.

Using histopathologic criteria, in 1931 Callender[1] divided uveal melanomas into six groups: spindle A, spindle B, fascicular, mixed, epithelioid, and necrotic. Subsequently, Callender and numerous other investigators[2–7] demonstrated the prognostic value of this classification. Currently, modifications of this classification are used in most ophthalmic pathology laboratories. However, it has not been universally accepted, and many aspects of the classification have been criticized.[8,9]

The spindle A group has received a large share of this criticism.[9] First, cells that many pathologists would consider benign nevus cells meet Callender's criteria for a spindle A melanoma cell. Secondly, Callender[1–3] defined neither the proportion of spindle A cells nor the cell types of the minority cell populations in spindle A melanomas. Thus, a spectrum of tumors could be classified as spindle A. These range from tumors composed purely of nevoid and bland spindle A cells to tumors with more atypical spindle A cells and a significant population of spindle B cells. Furthermore, many ophthalmic pathologists classify tumors containing occasional epithelioid cells among the spindle cell types. This practice would include tumors that contain epithelioid cells in the spindle A group.

The result of these problems and practices has been a blurring of the distinction between certain benign and malignant melanocytic tumors of the uvea. Previously, when all eyes containing melanocytic tumors were enucleated, a more precise separation of spindle cell nevi from spindle cell melanomas was entirely academic. Today, this distinction needs better definition because of current controversies concerning differential diagnosis and management of small uveal tumors and the related interpretation of results of various diagnostic procedures. We re-examine herein Callender's spindle A group of melanomas and formulate new histologic criteria in an attempt to distinguish more effectively between benign and malignant spindle cell tumors.

MATERIAL AND METHODS

The melanomas used in this study were selected from those in the Registry of Ophthalmic Pathology at the Armed Forces Institute of Pathology. In all cases the final histopathologic diagnosis before our study had been spindle A melanoma; the main tumor mass was in the choroid or ciliary body; the date of enucleation was before Jan. 1, 1966; adequate histologic material was available for re-evaluation; and follow-up information was obtained. The tumors were divided into three groups. The first group included tumors composed of slender nevoid, and benign appearing spindle A cells (Fig. 1, top) that measured no more than 10 mm in diameter and 3 mm in elevation and that had no mitotic activity, no necro-

From the Registry of Ophthalmic Pathology, Armed Forces Institute of Pathology, Washington, D.C. The opinions of assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, the Department of the Air Force, or the Department of Defense.

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Reprint requests to Lorenz E. Zimmerman, M.D., Department of Ophthalmic Pathology, Armed Forces Institute of Pathology, Washington, DC 20306.

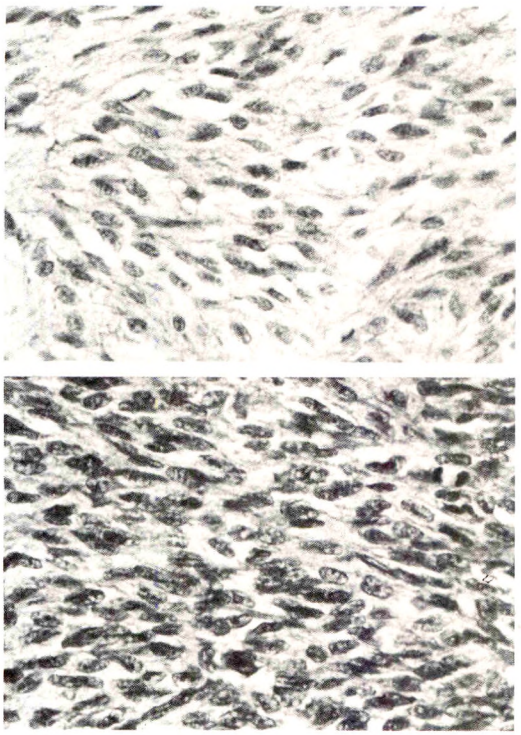


Fig. 1 (McLean, Zimmerman, and Evans). Comparison of benign cytologic features of tumor from Group 1 (top) with more malignant cytologic characteristics of fatal tumor (Case 11, Table 2) from Group 2 (bottom). Cells in the Group 2 tumor have plumper and more hyperchromatic nuclei with a higher nuclear to cytoplasmic ratio. Some cells have marginated chromatin and prominent nucleoli, features of Callender's spindle B type cells. Mitotic figure is present in upper right portion of field (hematoxylin and eosin, ×625).

sis, and no invasion of the sclera or subretinal space. The tumors in the second group were composed of more atypical spindle cells (increased nuclear to cytoplasmic ratio, clumped chromatin, and distinct nucleoli) (Fig. 1, bottom) and violated one or more criteria for inclusion in the first group. The third group of tumors included those in which epithelioid cells could be identified. The survival statistics for the three groups were computed by the actuarial life table method with an IBM-360-30 computer and the BMD-11S program.[10] Survival rates were compared by use of the Student *t*-test.

Results

In the Registry of Ophthalmic Pathology there were 132 tumors diagnosed as spindle A malignant melanoma of the choroid, ciliary body, or both, that met the criteria for our study. The actuarial mortality rates for these 132 tumors at five, ten, and 15 years were 3, 12, and 18%, respectively. Of the 105 cases with adequate histologic material available for us to review, 15 were small tumors confined to the choroid, ciliary body, or both, and were composed of benign appearing nevoid and spindle A cells without mitotic activity or necrosis (Group 1). The clinical appearance and histologic findings of one of these are shown (Fig. 2 and 3). No deaths were attributable to metastasis from the intraocular tumors in this group (Table 1). The second group was the largest (75 cases). All of these

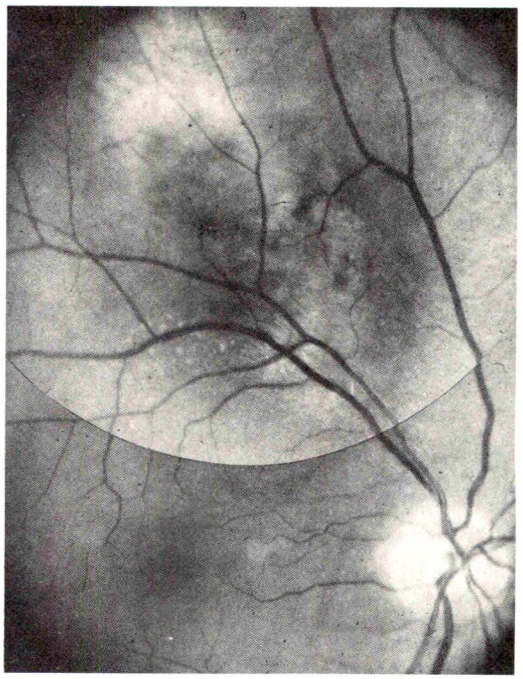


Fig. 2 (McLean, Zimmerman, and Evans). Spindle cell nevus (Group 1 tumor) originally diagnosed as spindle A melanoma. The tumor measures 4 × 3 disk diameters, is minimally elevated, and has mottling of overlying pigment epithelium and multiple drusen at its inferior border.

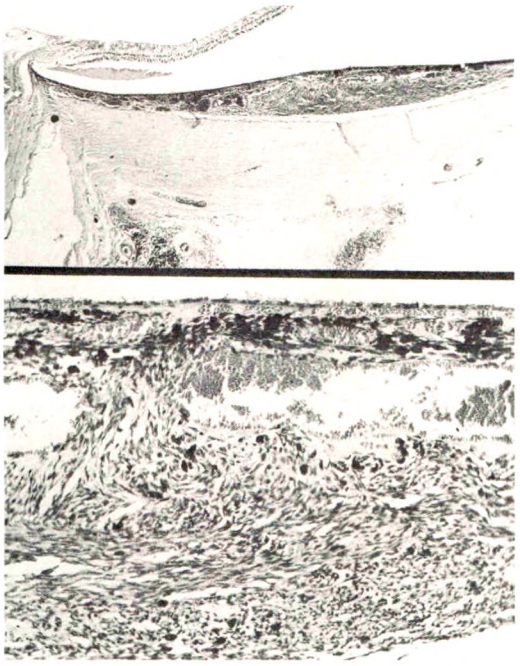


Fig. 3 (McLean, Zimmerman, and Evans). Histologic section through center of spindle cell nevus shown in Figure 2. Retina is detached over tumor with subretinal exudate adjacent to disk. Tumor is composed of bland spindle-shaped cells with sparing of choriocapillaris (hematoxylin and eosin; top, ×18; bottom, ×130).

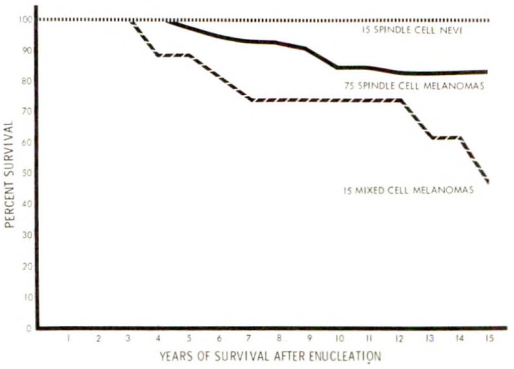


Fig. 4 (McLean, Zimmerman, and Evans). Actuarial survival for 105 patients with spindle A melanoma after re-evaluation and reclassification of cases. Nontumor deaths are excluded.

tumors contained cells more atypical than those in Group 1 (Fig. 1, bottom), and some of the cells were consistent with those of Callender's spindle B type. The proportion of spindle B cells was usually small, but occasionally exceeded 50%. This group of tumors had a relatively good prognosis (Table 1). In the third group the tumors all contained a small proportion of epithelioid cells. The prognosis for cases in this group was relatively poor (Table 1). The prognoses of the three groups are compared graphically (Fig. 4), and the mortality rates were found to be statistically different ($P < .05$) at 15 years.

There were no fatal tumors in Group 1. The gross and histologic features that differentiated lethal tumors from those in Group 1 are summarized (Table 2). The most consistent findings in the group of fatal tumors were large size and the presence of mitotic activity. Invasion of the tumor into the sclera or through Bruch's membrane was present in ten of the cases, epithelioid cells were present in seven,

TABLE 1

ACTUARIAL SURVIVAL FOR 105 PATIENTS WITH SPINDLE A MELANOMA AFTER RE-EVALUATION AND RECLASSIFICATION OF CASES

Group	Proposed New Designation	No. of Cases	No. of Tumor Deaths	Actuarial Survival (Percent ± S.E.*)		
				Five-Year	Ten-Year	15-Year
1	Spindle cell nevus	15	0	100 ± 0	100 ± 0	100 ± 0
2	Spindle cell melanoma	75	11	97 ± 2	84 ± 5	82 ± 5
3	Mixed-cell melanoma	15	7	87 ± 9	72 ± 12	45 ± 17

*S.E. designates standard error.

TABLE 2

HISTOLOGIC FEATURES AND DOCUMENTATION OF METASTASIS IN 18 FATAL CASES

Case No.	Tumor Size(mm) (Diameter × Elevation)	Group	Mitotic Figures per 40 high power fields	Necrosis	Invasion	Documentation of Metastasis
1	16 × 11	2	2	None	Retina	Autopsy
2	13 × 7	3	1	None	Retina	None
3	11 × 8	2	6	None	Sclera	None
4	10 × 10	3	0	None	Retina	None
5	14 × 11	2	5	None	Retina	None
6	7 × 3	2	8	None	None	None
7	10 × 8	2	4	None	None	None
8	15 × 6	3	5	Extensive	None	None
9	12 × 8	2	2	None	Retina	None
10	16 × 10	3	5	None	None	Autopsy
11	11 × 10	2	3	Focal	Sclera and retina	Liver biopsy
12	11 × 10	2	1	Focal	Sub-retinal	Liver biopsy
13	11 × 8	2	2	None	None	Bone biopsy
14	11 × 9	3	2	None	None	None
15	17 × 4	3	3	None	Sclera	None
16	14 × 10	2	1	None	Retina	Autopsy
17	13 × 5	2	5	None	None	Autopsy
18	10 × 2	3	2	None	None	Liver biopsy

and necrosis was present in three. In eight of the 18 fatal cases, metastasis was documented by either biopsy or autopsy.

DISCUSSION

The pathologist has tended to agree with the ophthalmologist's assumption that if a melanocytic tumor grows sufficiently large or produces complications, it must be a malignant melanoma. Therefore, when Callender[1] first described the cell types he found in 111 uveal tumors, he assumed that because the tumors all had led to enucleation, they must have been malignant. Callender, Wilder, and Ash[1-3] gave no histologic criteria for distinguishing between benign and malignant spindle melanomas. In the design of our study, we believed such criteria should be defined. Based on our experience with iridic, conjunctival, and cutaneous melanocytic tumors, we hypothesized that a choroidal tumor fulfilling the following criteria should be considered benign: (1) the constituent cells exhibit a low nuclear to cytoplasmic ratio; (2) the nuclear chromatin is fine and the nucleoli are small or absent; (3) the tumor measures less than 10 mm in diameter and 3 mm in elevation; (4) it does not invade the sclera or rupture Bruch's membrane; and (5) there is no mitotic activity or necrosis within the tumor. When we reviewed the 105 tumors classified as spindle A, 15 met the above criteria. Follow-up on these 15 cases revealed no tumor deaths. We concluded that such tumors are benign and that they had been classified incorrectly as malignant melanomas.

In addition to having failed to provide histologic criteria to distinguish spindle A melanomas from nevi, Callender[1-3] also did not provide in his publications criteria for classification of a tumor composed of a mixture of spindle A and B

cells. Our review of the Registry cases revealed that most tumors originally classified as spindle A did contain spindle B cells; these 75 cases comprise our Group 2. The percentage of spindle B cells ranged from less than 1% to approximately 50%. The old records pertaining to one case include a comment made by Callender that reveals what his criteria were for division of spindle cell melanomas into A & B types. He stated, "This (tumor) is sort of a transition stage between A and B. Nearly 50% (of the cells) have pretty good nucleoli and it is pretty cellular for an A." Callender nevertheless classified this tumor as a spindle A type of melanoma; yet when sections of the tumor (Fig. 5) were reviewed by the current staff here, all classified the tumor as belonging in the spindle B group.

The change in classification of uveal melanomas here toward a more restrictive definition of spindle A melanoma is reflected by the decreasing incidence of the spindle A designation in the Registry file. In his initial review of 111 tumors, Callender[1] classified 10% as spindle A. Eleven years later, Wilder, and Ash[3] classified 6.6% (33) of 500 tumors as spindle A.

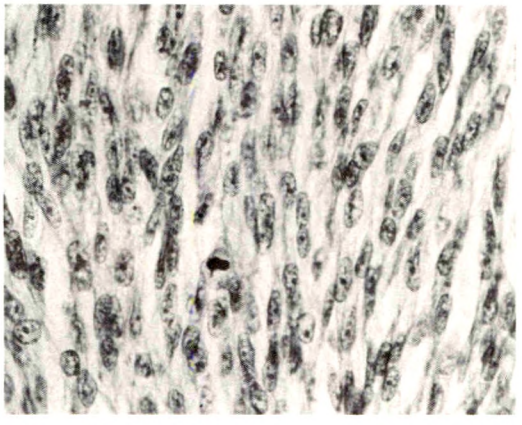


Fig. 5 (McLean, Zimmerman, and Evans). Malignant melanoma studied and classified as spindle A by Callender. At least 50% of cells are of spindle B type and a mitotic figure is present (hematoxylin and eosin, ×660).

Paul, Parnell, and Fraker[5] reported only a 4.7% (126) incidence among 2,652 tumors. In addition to the cases reported by Paul, Parnell, and Fraker,[5] our study included others in which enucleation was performed between 1956 and 1965. The incidence rate during this ten-year period decreased to 2.2%.

In our review of the 105 melanomas, we found that 15 tumors contained a small proportion of epithelioid cells. We concluded that the relatively high rate of tumor-related deaths in this group justified reclassification of these tumors as the mixed-cell type.

The presence of tumors we would currently classify as mixed-cell type within the group previously classified as spindle A type probably results from several factors. The first is that the pathologist who studied the slides initially either may have missed small foci of epithelioid cells or thought that their numbers were too few to justify placement of the tumor in the mixed-cell category. The second and probably more important factor is that over the years, the definition of an epithelioid cell may have changed. The variability among ophthalmic pathologists in their assignment of cell types of choroidal melanomas is documented by the studies of Gamel and McLean[11] and by Gass.[9] These investigators found a high rate of disagreement between ophthalmic pathologists in the classification of both melanoma cells and uveal melanomas.

Gass[9] questioned whether any patient had ever died from a melanoma composed purely of spindle A and B cells. He hypothesized that deaths attributed to metastasis in patients with spindle cell types of melanomas were either the result of metastasis from hidden foci of epithelioid cells within the tumor or the result of metastasis from a secondary primary tumor.

In our study, in 11 cases no epithelioid cells were found on review of the histo-

logic material and death was attributed to metastatic melanoma from the eye. In six of these cases the cause of death was confirmed by either biopsy or autopsy, which eliminates the possibility of death having been the result of some other cancer. Gass's[9] first hypothesis is virtually impossible to test because without serial sections of the entire tumor, it is impossible to rule out the presence of a small focus of epithelioid cells. In our study, serial sections of the entire tumor were not available. However, there were multiple levels for most cases, and in one case with metastasis documented by liver biopsy (Table 2, Case 11), we examined more than 100 serial sections without finding any epithelioid cells.

The most convincing evidence that spindle cells in uveal melanomas do metastasize is from examination of metastatic foci. Spindle cells are frequently observed in metastatic melanoma, and a focus in the liver from one of our cases (Table 2, Case 16) was composed of a pure population of spindle A cells (Fig. 6). Because an epithelioid cell probably would not produce a pure population of spindle A cells after metastasis, we believe that both spindle A and spindle B melanoma cells have some potential for producing metastatic disease, at least after enucleation.[12] The better prognosis for spindle cell tumors when compared with that of tumors of mixed-cell type indicates a profound biologic difference in the malignant potential of spindle and epithelioid melanoma cells.

Our conclusion from this study is that a revision of Callender's classification is justified. The benign tumors in Group 1 should no longer be classified as malignant melanomas. We propose that they be called spindle cell nevi. The unquestionably malignant tumors in Group 3 should be put into the mixed-cell category. The tumors in Group 2 are not clearly different from spindle B tumors either in composition or in prognosis. They usually contain spindle B cells in addition to spindle A cells, and they have an 18% mortality at 15 years, a survival rate only slightly better than that of other spindle B melanomas. We propose that they and the more typical spindle B tumors be grouped together under the designation "spindle cell malignant melanoma." This revision makes two improvements on the Callender classification. First, it simplifies the classification by the elimination of the arbitrary distinction between spindle A and spindle B types. Although there is a spindle A cell and a spindle B cell, malignant melanomas composed of spindle cells almost invariably have a mixture of these two types. Secondly, it makes a histologic distinction between nevi and melanomas.

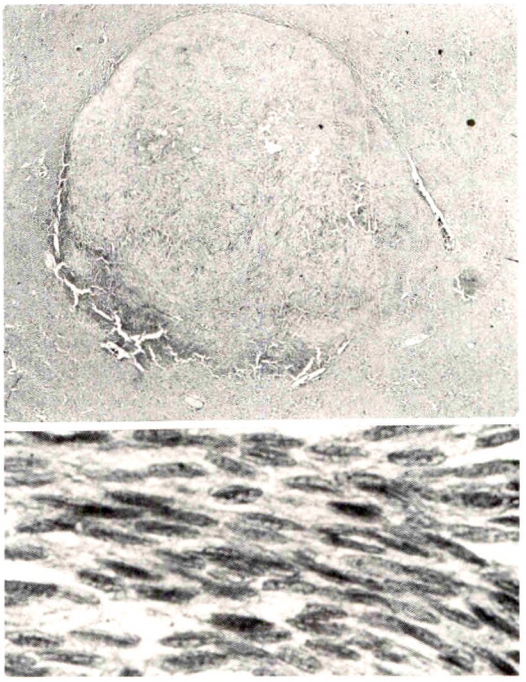


Fig. 6 (McLean, Zimmerman, and Evans). Metastatic tumor nodule in the liver composed of Callender's spindle A type cells (hematoxylin and eosin; top, ×6, bottom, ×600).

Gass[9] pointed out that most clinical

criteria for a malignant melanoma are not absolute indicators of malignancy. One of the stimuli for us to undertake our study has been a dramatic increase in the number of eyes enucleated with small melanocytic choroidal tumors. In many of these cases, the histologic features were indicative of spindle cell nevi. The findings in eight of these recent cases are summarized (Table 3). These cases support Gass's[9] contention that the differentiation of small melanomas from large nevi is difficult and often impossible on the basis of currently available clinical techniques and tests. The phosphorous uptake (^{32}P) test was considered positive in each of these eight cases by the referring ophthalmologists who often indicated this as a major factor in their decision to enucleate. We believe ophthalmic pathologists are largely responsible for these unnecessary enucleations. If pathologists had been less complacent in the past about calling benign tumors spindle A melanomas, ophthalmologists would not have arrived at the erroneous conclusion that the ^{32}P uptake test is highly reliable for differentiating nevi and small melanomas.[13–15] We believe ophthalmologists should show greater reluctance in advocating enucleation of an eye with a small, minimally elevated melanocytic lesion and good visual acuity. They cannot rule out the possibility that such a lesion is a nevus, and there is no evidence that harm is done the patient by observation of these tumors even if they subsequently should prove to be malignant melanomas.

A number of questions still need to be answered before an optimum treatment

TABLE 3

CLINICAL FINDINGS IN EIGHT RECENT CASES OF SPINDLE CELL NEVUS

Case No.	Size (mm) Diameter × Elevation	^{32}P Uptake Test Results	Observed Growth	Visual Acuity	Retinal Detachment
1	7 × 0.5	109%	None	6/6 (20/20)	No
2	6 × 0.5	62%	None	6/6 (20/20)	No
3	3 × 0.5	100%	None	6/6 (20/20)	Yes
4	9 × 1.0	186%	Slight*	6/6 (20/20)	No
5	7 × 0.5	207%	Slight	6/12 (20/40)	No
6	8 × 0.5	100%	None	NS†	Yes
7	5 × 0.5	60%	Slight*	6/6 (20/20)	No
8	5 × 0.5	120%	Slight	6/60 (20/200)	Yes

*Growth not documented photographically.
†Not stated.

regimen can be devised for malignant melanoma. The most important of these is how often do small melanocytic tumors of the choroid (tumors measuring less than 10 mm in diameter and 3 mm in elevation) grow into really large intraocular tumors and how often do these metastasize in the absence of surgical intervention? We hope our work will provide an additional stimulus for cooperation among the ophthalmic community as advocated by Gass[9] to answer these questions.

Summary

A follow-up study and histologic reevaluation were made of 105 melanomas of the choroid and ciliary body that had originally been classified as Callender's spindle A type. There were 18 deaths attributable to tumor, with metastatic disease confirmed by autopsy or biopsy in eight cases. We were able to separate the 105 melanomas histopathologically into three groups. The first group consisted of 15 cases in which the spindle-shaped tumor cells were cytologically benign; no deaths were observed for this group. The 75 tumors in the second group were composed of spindle cells, but differed from those in the first group by their malignant features, namely, more atypicality of cells, mitotic activity, necrosis, invasion into sclera or through Bruch's membrane, larger size of the tumor, or any combination of the above. The prognosis for this group was good, comparable to that of spindle B melanomas. The 15 tumors in the third group contained epithelioid cells and had a poor prognosis, comparable to that of mixed-cell melanomas.

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INTRAOSSEOUS HEMANGIOMA OF THE ORBITAL ROOF

HOWARD J. GROSS, M.D., AND ALAN M. ROTH, M.D.
Davis, California

Whereas hemangiomas are the most common primary tumors of orbital soft tissue,[1–3] hemangiomas of orbital bone are unusual. Yet these tumors are expansile and can cause proptosis, restricted ocular motility, and visual loss.

Because of their distinctive radiographic appearance, many descriptions of osseous hemangiomas have been published in radiology journals[4–13]; however, we have been able to find only two reports of this lesion in ophthalmic journals. Mortada[14] described a patient with proptosis and optic atrophy who had a mass in the bony orbit. Biopsy of this lesion showed it to be an osseous hemangioma. Clay and associates[15] reported the only other case: an infant who had displacement of her left eye and mild limitation of extraocular movements. Diagnosis in this case was also made after surgical biopsy. We describe herein a case of osseous hemangioma of the bony orbit.

CASE REPORT

We first saw a 63-year-old woman because of bilateral blurred near vision. She had noted a painless mass gradually growing over her left eye for the previous five years but denied orbital trauma, diplopia, pain, or headache. She had sustained a tripod fracture of the left ankle one year previously. She had no history of hematologic or neurologic disorders. Examination showed her best visual acuity as R.E.: 6/6 (20/20); L.E.: 6/6-1(20/20-1); near vision was correctable to Jaeger 1 in both eyes. Visual fields were full to confrontation and Amsler grid showed no central defect. Pupils were 3.5 mm in the right eye and 3 mm in the left with normal reaction; no afferent pupillary defect was present. Muscle balance was normal with full ductions of each eye.

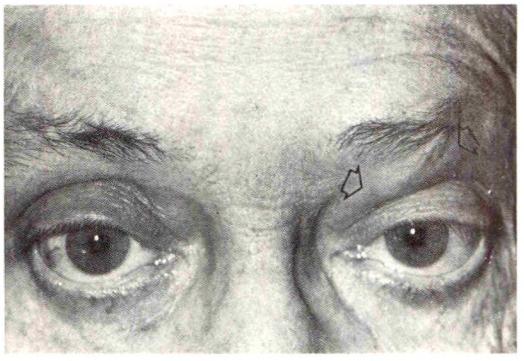


Fig. 1 (Gross and Roth). Firm, slightly tender 25 × 15-mm nodule fixed to left supraorbital rim (arrows) with free movement of overlying skin. Globe is not displaced and motility is full.

Slit-lamp examination showed normal anterior segments except for mild nuclear sclerosis of each crystalline lens. Examination of the ocular fundi was normal.

A 25 × 15-mm firm, slightly tender nodule was fixed to the left supraorbital rim (Fig. 1). We could move the skin freely over the mass, and we did not hear bruits or feel pulsations.

Complete blood cell count, urinalysis, and blood chemistry studies all were within normal limits. Orbital radiographs revealed a spiculated lesion in the outer table of the left frontal bone that protruded into the left orbit and frontal sinus and deformed the left supraorbital rim (Fig. 2). Lateral projection showed the spicules formed a sunburst pattern typical of osseous hemangioma (Fig. 3).

The lesion was excised surgically by an en bloc resection of the left frontal bone including the supraorbital ridge. The supratrochlear neurovascular bundle was dissected free and spared. The



Fig. 2 (Gross and Roth). Skull radiograph shows mass deforming left supra orbital rim and protruding into orbit. Fine reticulated structure forms honeycomb pattern; no hyperostosis is present.

From the Departments of Ophthalmology (Drs. Gross and Roth) and Pathology (Dr. Roth), School of Medicine, University of California, Davis, and the UCD-Sacramento Medical Center, Sacramento, California.

Reprint requests to Alan M. Roth, M.D., 251 UCD Professional Bldg., 4301 X St., Sacramento, CA 95817.



Fig. 3 (Gross and Roth). Lateral projection shows radial striations in sunburst pattern typical of osseous hemangioma.

opened frontal sinus was obliterated with abdominal fat and temporalis muscle and fascia and the bony defect closed with a molded methyl methacrylate plate. Postoperative recovery was good, and the patient has no ocular or other residua.

Results

The specimen consisted of a portion of bone 25 mm in diameter with a 20-mm rounded, raised purplish mass located centrally (Fig. 4). Multiple crateriform depressions were seen on its surface. The posterior aspect (Fig. 5) showed many bright red blood-filled spaces enclosed by coarse, bony trabeculae. Radiograms of the specimen confirmed the honeycombed appearance with sunburst pattern of the bone.

Histologic sections (Fig. 6) showed normal appearing bony trabeculae surrounding large stromal lucunae which contained generally uniform-sized cavernous vascular channels lined by flattened endothelial cells and filled with blood. A thick fibrocellular matrix enclosed these channels (Fig. 7) and contained scattered lymphocytes. In a few areas, endothelial cell proliferation and finer capillary-sized channels were present (Fig. 8). We saw occasional osteoclasts and rare osteoblasts at the margins of the bony spicules.

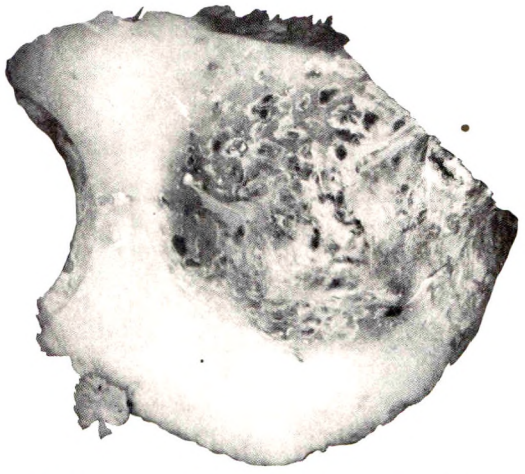


Fig. 4 (Gross and Roth). Anterior surface of gross specimen. Purple, raised, rounded mass has multiple crateriform depressions. Histologic sections taken from upper right side.

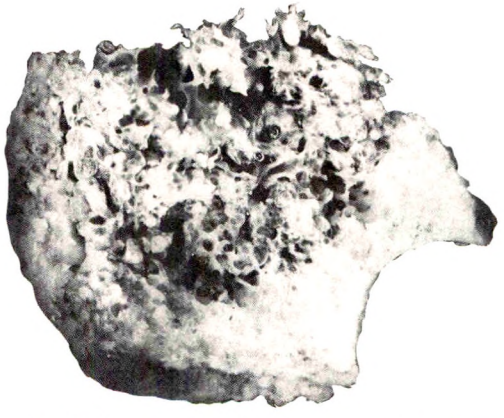


Fig. 5 (Gross and Roth). Posterior surface of gross specimen. Coarse, bony trabeculae enclose blood-filled spaces.

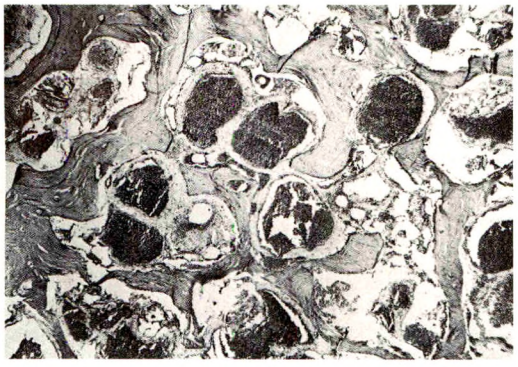


Fig. 6 (Gross and Roth). Blood-filled vascular channels are uniform in size and surrounded by normal appearing bony trabeculae (hematoxylin and eosin, ×20).

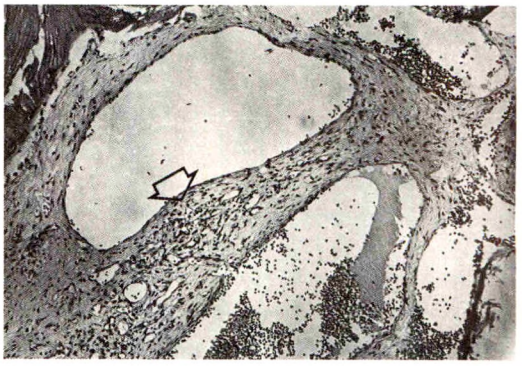


Fig. 8 (Gross and Roth). Focal endothelial cell proliferation with finer capillary-size channels (arrow) (hematoxylin and eosin, ×80).

Discussion

Osseous hemangioma is a benign primary tumor of bone arising from its intrinsic vasculature. It is a rare tumor comprising less than 1% of all primary bone neoplasms[9,16] and occurs more frequently in the vertebral column than in all the other bones of the body together.[4] The skull is the most common extravertebral site; Bucy and Capp[4] found the tumor in the skull in 54.5% of osseous hemangiomas not in vertebrae. Geschickter[17] reported the incidence of hemangioma of bone was 12.8% of primary benign skull tumors he studied. Wyke[9] identified 40 reports of primary hemangiomas of the skull; of these, less than half were in the parietal bone and less than one fourth in the frontal bone; 4½% involved the bony orbit. They were most common in the fourth decade of life and three times more common in females than in males. There was frequently a history of trauma to the involved area.

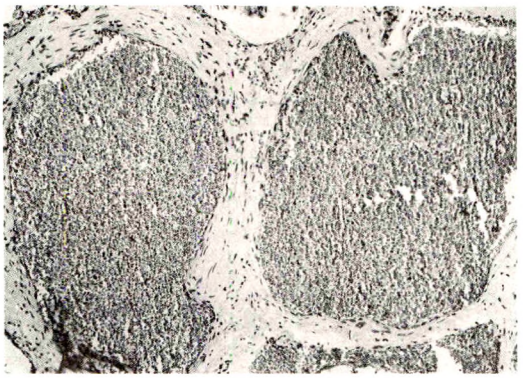


Fig. 7 (Gross and Roth), Vascular spaces are lined by flattened endothelial cells and enclosed by thick fibrous stroma (hematoxylin and eosin, ×80).

Extracranial osseous hemangiomas often are asymptomatic. However, patients usually notice cranial lesions as a palpable and often visible mass, which may be tender. As the lesion expands, it may cause severe and frequent headaches and other symptoms of increased intracranial pressure. Orbital lesions, however, cause local signs and symptoms much earlier.[9,14,15,18,19] These include decreased vision, local pain, diplopia, nonaxial proptosis, extraocular muscle dysfunction, blepharoptosis, fifth nerve deficit, papilledema and optic atrophy. Because the mass in our patient had expanded predominantly anteriorly rather than further into the orbit, she had no ocular signs, but only slight tenderness. The patient denied trauma to the area. Trauma has been implicated in the pathogenesis of these lesions,[20] but the absence of it in

this case makes its influence questionable and reinforces the probability that they are hamartomas like their soft tissue counterparts.

Because of the lack of suggestive signs and symptoms, diagnosis in the present case was not suspected until radiologic study was done. The roentgenologic appearance of hemangiomas of the skull is typical[12] and is the principal means of diagnosis[9]: a single area of rarefaction, round to oval and 1 to 7 cm in diameter. A characteristic internal pattern consists of fine striae or reticulations forming a honeycomb pattern (Fig. 2). Tangential or profile views are necessary in the radiologic study[12] (Fig. 3) and often show radial striations forming a sunray appearance: the outer bony table may be eroded, but the inner table is usually intact with no reactive sclerosis or hyperostosis. Cases have been reported in which contrast studies have been performed; these are unnecessary because the appearance on plain films is generally indicative on careful study.[9]

The x-ray film appearance may be confused with that of meningioma if superficially examined. However, whereas meningiomas may produce striations and stippled eroded areas in bone, the striations are vertical and parallel instead of radiating in a sunburst pattern as in hemangiomas. Moreover, meningiomas usually produce reactive sclerosis or hyperostosis, and they erode the skull from within, affecting the inner table more than the outer. Other conditions that may produce rarefied areas on skull radiographs (osteoma, epidermoid or leptomeningeal cyst, xanthomatosis, myeloma, intracranial hemangioma, metastatic carcinoma) generally have sufficient differentiating characteristics so as not to cause major difficulties in diagnosis.

Treatment of osseous hemangiomas of the orbit is surgical. Block resection removes the lesion intact and is uncomplicated, and recurrence is not a problem. Radiotherapy can be done, but is seldom indicated unless the tumor is surgically inaccessible. Without treatment, the tumor will grow and increasingly encroach on orbital, intracranial structures, or both, and can prove fatal.[6,9] However, Anspach[21] observed a case for 15 years after an unsuccessful attempt at resection and noted no signs or symptoms of intracranial extension.

On pathologic study, osseous hemangiomas are usually of the cavernous type as in our case; rarely is the capillary form seen.[19,22] These are benign tumors; Anspach[21] observed his patient for 15 years and Rowbotham[18] observed two patients who had incomplete excisions for four years without evidence of recurrence or metastasis. Primary malignant bone tumors of vascular origin are rare.[23] Hemangiopericytomas, both benign and malignant, may arise within bone. Clay and associates[15] cited a report by Zimmerman of a case of hemangioendothelioma of frontal bone. Steiner and Dorfman[24] stated that these tumors are invariably malignant. Osseous hemangiomas strongly resemble their soft tissue counterparts. The most striking difference is the abundant trabecular bone between the thick connective tissue stroma that surrounds the vascular spaces. These trabeculae are not part of the primary hamartomatous pattern, but are secondary to reactive bone destruction and formation.[18] Blodi[25] noted that lesions of the bony orbit are not "discussed as extensively and intensively as they deserve to be" because they are rare and require special knowledge for pathologic interpretation. Although Blodi mentions the case of orbital hemangioendothelioma described by Zimmerman, he does not discuss osseous hemangioma.

SUMMARY

A 63-year-old woman had an osseous hemangioma of the orbital rim. Diagnosis of this primary bone tumor was made by

its distinctive radiographic appearance and confirmed by pathologic examination. Although this is a benign lesion, it is expansile and can cause ocular signs. Surgical resection is the recommended treatment.

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NOTES, CASES AND INSTRUMENTS

THE MECHANISM OF THE MIOCHOL LENS OPACITY

N. ROSEN, M.D., AND M. LAZAR, M.D.
Tel-Aviv, Israel

We recently reported the occurrence of lens opacities following the intracameral injection of Miochol.[1] Such lens opacities have also been observed by other investigators.[2] Because Miochol is a hyperosmotic solution (containing 20 mg of acetylcholine and 100 mg of mannitol in 2 ml water), we postulated that these lens opacities are caused by an osmotic effect. We studied this hypothesis in the following experiments.

MATERIAL AND METHODS

We used adult rabbits weighing 4 to 6 kg. The rabbits were anesthesized with an intravenous injection of nembutal, and both pupils were dilated with 10% phenylephrine and 1% atropine. The lenses were examined with the slit lamp before paracentesis of the anterior chamber. Ten microliters of aqueous was withdrawn through the corneoscleral limbus with a 25-gauge needle, and immediately, a solution of known osmolarity containing acetylcholine, mannitol, or both, was injected in the anterior chamber (Table). The second eye served as control and its anterior chamber was injected with normal saline. Each eye was used for one experiment only. The lenses were examined under the slit lamp 10, 20, 40, 60, and 120 minutes after injection. Daily examination was performed during the following five days.

RESULTS

All lenses irrigated with the commercially available hypertonic Miochol developed opacities (Table). The opacities appeared ten to 20 minutes after injection of the solution and disappeared one to two hours later. Opacities did not appear in any of the lenses irrigated with diluted Miochol. No lens opacities were observed when the anterior chamber was irrigated with acetylcholine 1% or mannitol 5%. Concentrated Miochol and hypertonic solutions of mannitol or acetylcholine caused dense lens opacities. All lens opacities disappeared within two hours, and the lenses remained clear during the entire follow-up. All control lenses remained clear.

DISCUSSION

Miochol is a hypertonic solution with an osmolarity of 390 mOsm, the osmolarity of the aqueous being only 300 mOsm. The results of the experiments clearly demonstrate that the lens opacities observed are caused by an osmotic effect. Acute reversible cataract caused by osmotic changes has been described in animals,[3-8] in incubated lenses,[3] and in humans.[9] Recently, Mester, Stein, and Koch[2] produced opacities in the rabbit lens by the intracameral injection of 1% and 5% acetylcholine. The lens opacities they described are similar to the ones observed in this study. Because they used hypertonic solutions, the acetylcholine being dissolved in balanced solvent, the "acetylcholine cataract" referred to by them is probably of an osmotic nature. In our

From the Department of Ophthalmology, Ichilov Hospital, Tel-Aviv, Israel.
Reprint requests to M. Lazar, M.D., Department of Ophthalmology, Ichilov Hospital, Tel-Aviv, Israel.

TABLE

THE EFFECT OF TONICITY OF INTRACAMERAL SOLUTIONS ON THE LENS

No. of Rabbits	Solution Injected	Calculated Osmolarity of Solution	No. of Lenses that Developed Opacities
8	Miochol (20 mg of acetylcholine chloride and 100 mg of mannitol in 2.0 ml of water	388 mOsm/l	8
4	1% acetylcholine chloride (20 mg of acetylcholine chloride in 2 ml of water)	111 mOsm/l	0
4	5% mannitol (100 mg of mannitol in 2 ml of water)	277 mOsm/l	0
4	Diluted miochol (20 mg of acetylcholine chloride and 100 mg of mannitol in 2.5 ml of water)	311 mOsm/l	0
4	Concentrated Miochol (20 mg of acetylcholine chloride and 100 mg of mannitol in 1.0 ml of water)	776 mOsm/l	4
4	5% acetylcholine chloride (100 mg acetylcholine chloride in 2.0 ml of water)	555 mOsm/l	4
4	15% mannitol (300 mg mannitol in 2.0 ml of water)	831 mOsm/l	4
32	Saline	283 mOsm/l	0

study 1% acetylcholine dissolved in distilled water had no effect on the lens. The lens opacity observed by us and by Mester, Stein, and Koch[2] after the intracameral injection of hypertonic acetylcholine solution proved to be reversible both clinically and experimentally. The late effect, if any, of this transient osmotic insult to the lens is unknown. It therefore seems desirable to avoid the injection of hypertonic solutions into the phakic eye.

SUMMARY

We studied the reversible cataractogenic effect of Miochol on rabbits' lenses. The experiments demonstrated that the lens opacities developing after the intracameral injection of Miochol were caused by the hypertonicity of the solution and not by a biochemical effect of the acetylcholine.

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CYSTOID MACULAR EDEMA AFTER CRYOTHERAPY

RONALD W. KIMBALL, M.D.,
PETER H. MORSE, M.D., AND
WILLIAM E. BENSON, M.D.
Philadelphia, Pennsylvania

Cystoid macular edema is a known complication of cataract extraction, aphakic penetrating keratoplasty, photocoagulation, glaucoma filtering operations, and pars plana vitrectomy.[1–3] In rhegmatogenous retinal detachment, the detached macula can become cystoid. Ryan[2] reported two cases of cystoid macular edema in patients whose maculas were not detached and who had had scleral buckling procedures and cryotherapy. We report herein the first known case of cystoid macular edema after cryotherapy alone.

CASE REPORT

A 50-year-old man had entopsias in the right eye of one week's duration. Visual acuity was 6/6 (20/20) in both eyes with a refractive error of R.E.: $-7.25 \times 0.50 \times 175$; L.E.: $-7.75 \times 0.75 \times 175$. The intraocular pressure was R.E.: 12 mm Hg; L.E.: 15 mm Hg. Ophthalmoscopic examination of the right eye (Fig. 1) showed four superonasal horseshoe tears with subclinical retinal detachment, a small operculated round hole at the 7 o'clock meridian, a small horseshoe tear at the 8 o'clock meridian, and a superotemporal area of chorioretinal atrophy. A small hemorrhage overlay the superonasal horseshoe tears. The left eye was normal. The patient was in good health and took no medication. His blood pressure was 122/84 mm Hg. Blood glucose was normal.

The chorioretinal atrophy and all tears were surrounded with cryotherapy. A superonasal incision in the conjunctiva and Tenon's capsule was necessary for treatment of the posteriorly located tears. Postoperatively, the patient received homotropine 5% twice daily for one week and prednisolone acetate 1% four times daily for two weeks. Five weeks after treatment, the patient returned complaining of poor vision in the right eye. Visual acuity was 6/9 (20/30) and improved to 6/7.5 (20/25) with pinhole. The anterior chamber had no cells or flare. The retinal breaks were well surrounded with cryotherapy. Cystoid macular edema was seen on clinical examination and was confirmed by fluorescein angiography (Fig. 2).

Two months later the visual acuity had returned to 6/6 (20/20), but the patient still complained of "blurred and faded vision." The cystoid macular edema had resolved, but there was wrinkling of the internal limiting membrane in the macula.

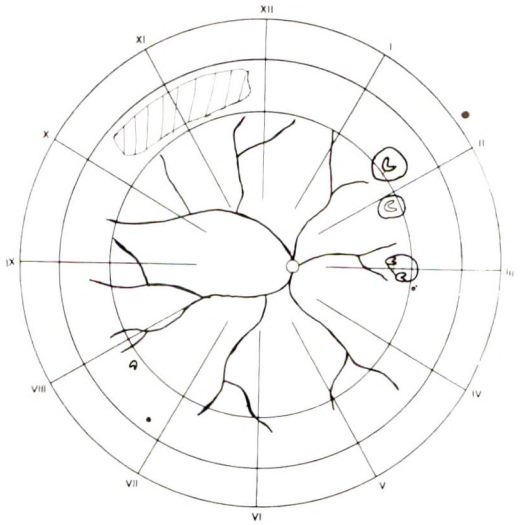


Fig. 1 (Kimball, Morse, and Benson). Drawing of right fundus before cryotherapy.

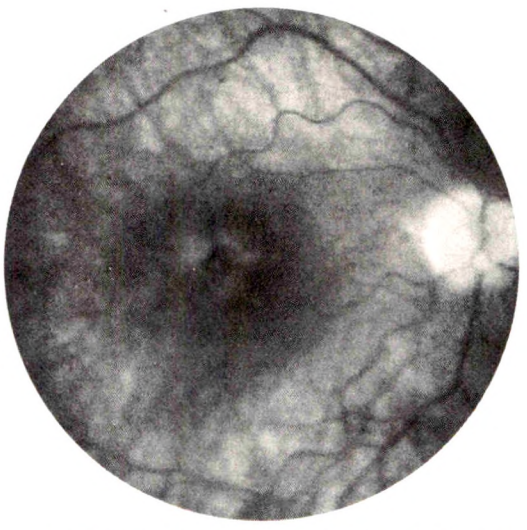


Fig. 2 (Kimball, Morse, and Benson). Right eye, late phase of fluorescein angiogram. Cystoid macular edema is present.

From the Retina Services of the Wills Eye Hospital (Dr. Benson) and the Scheie Eye Institute (Drs. Kimball and Morse), Philadelphia, Pennsylvania.

Reprint requests to William E. Benson, M.D., 187 East Evergreen Ave., Philadelphia, PA 19118.

DISCUSSION

This case demonstrates that cystoid macular edema can occur following cryotherapy alone. The patient had no predisposing conditions for cystoid macular edema, such as hypertension, diabetes, uveitis, or aphakia. His postoperative course was uneventful except for the resultant cystoid macular edema and subsequent cellophane maculopathy. Because cystoid macular edema has never been reported as accompanying untreated retinal breaks, it seems that in this case, it was caused by the cryotherapy. The mechanism is not known. Choroidal necrosis may have caused diffuse, low-grade intraocular inflammation, which indirectly affected the posterior pole.

Treatment was surely justified for this patient's fresh flap tears, but the resultant cystoid macular edema indicates that cryotherapy is not a completely harmless procedure. Its use should be carefully weighed in each case.[4]

SUMMARY

A 50-year-old man developed cystoid macular edema five weeks after cryotherapy of acute retinal tears. The cystoid edema cleared spontaneously, but ultimately the fovea developed wrinkling of the internal limiting membrane.

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MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

THE EUROPEAN OPHTHALMIC PATHOLOGY SOCIETY

The European Ophthalmic Pathology Society held its Annual Meeting in Belgrade, Yugoslavia, June 14-17, 1978. A. P. Ferry (Richmond, Virginia, United States) was the guest of honor. The scientific program included 39 case presentations by members and guests and 17 nations were represented. For each presentation, a protocol, histopathologic sections, and appropriate clinical or macroscopic transparencies were provided.

The majority of case presentations dealt with benign or malignant neoplastic processes involving the globe, orbit, or eyelid and the discussion was concerned predominantly with classification, prognosis, and management. Congenital malformations were also a prominent feature among the presentations and the remainder of the cases provided examples of systemic disorders involving ocular or adnexal tissues.

The 31 members who attended were: S. Ry Andersen (Denmark); K. Arnesen (Norway); N. Ashton (United Kingdom); J. Babel (Switzerland); E. Balestrazzi (Italy); D. R. Barry (United Kingdom); M. Brihaye-van Geertruyden. (Belgium); A. Brini (France); B. Daicker (Switzerland); P. Dhermy (France); P. C. Donders (Holland); H. Fanta (Austria); A. Garner (United Kingdom); A. Hamburg (Holland); M. Hanssens (Belgium); A. Henriquez (Spain); O. A. Jensen (Denmark); E. Landolt (Switzerland); W. R. Lee (United Kingdom); O. Litricin (Yugoslavia); O. -E. Lund (West Germany); W. A. Manschot (Holland); J. Mullaney (Ireland); G. O. H. Naumann (West Germany); A. H. Nover (West Germany); M. Quintana (Spain); R. Seitz (West Germany); F. H. Stefani (West Germany); A. Tarkkanen (Finland); D. Toussaint (Belgium); and M. Vogel (West Germany).

Professor P. Bec (France); Professor J. G. Cunha Vaz (Portugal); Dr. E. Kock (Sweden), and Dr. G. Morgan (United Kingdom) were unable to attend.

The seven guests attending were: G. Goder (East Germany); R. Haddad (Austria); E. N. Hinzpeter (West Germany); Z. Latković (Yugoslavia); P. Naeser (Sweden); A. H. S. Rahi (United Kingdom); and H. E. Völcker (West Germany). P. Dhermy (France) was elected president, and W. R. Lee (United Kingdom) was elected corresponding secretary of the Society.

Professor Olga Litricin acted as hostess for the meeting and her excellent organization also provided a stimulating and enjoyable social program.

The next meeting of the society will be held in Brussels, Belgium, with D. Toussaint as organizing secretary.

NORMAN ASHTON

INTERNATIONAL INTRA-OCULAR IMPLANT CLUB—FIFTH MEETING

The fifth meeting of the International Intra-Ocular Implant Club was held in Nagoya, Japan, on May 22 and 23, 1978, at the invitation of the Japan Intra-ocular Implant Society under the chairmanship of Professor S. Hayano of Gifu.

The proceedings were opened with a message from Harold Ridley, the originator of intraocular lens implantation, whose name has been commemorated by the institution of the Ridley Medal Lecture. The first of these lectures on the subject of the evolution of the anterior chamber implant up to and including the

Choyce Mark IX was delivered by D. P. Choyce, the recipient of the 1978 Ridley Medal.

Separate sessions of papers devoted to reports of methods and results in anterior chamber (Tennant, Hurt, and Wilson) pupillary (Singh and Christie) and anterior chamber implantation (Krasnov, Harris, Arnott, and Freeman) followed, and it was obvious that no concensus exists yet on the safest or most efficacious method of achieving pseudophakia. Stabilization of the lens within the eye was stressed and pupillary lenses were criticized because of their greater mobility than other styles. Great importance was placed on avoiding endothelial damage at the time of lens insertion, and "closed" eye methods were advocated by many speakers.

One session concentrated on the management and avoidance of complications in intraocular lens surgery and several papers reported good results from keratoplastis both combined with cataract extraction and implantation, and as a secondary procedure for corneal decompensation after lens implantation (Reshni, Taylor, and Gould). Controversy remains over the high incidence of cystoid macular edema after various methods of pseudophakia. Evidence for the role of prostaglandin secretion in the incidence of this complication was adduced in a paper by Ozaki from Japan, which demonstrated a lowered incidence after topical indomethacin administration. Bobberg-Ans and Shepard discussed complications in detail. Their papers were well received for their valuable contributions in indicating the need for proper caution and a conservative approach to the use of lens implants. Drews described persisting glaucoma to be a relative contraindication.

A final group of papers concentrated on the rate of pseudophakia in the third world, and stimulated a vigorous discussion and much interest in the course of which the club decided to indicate its intention to work actively towards the development of a safe, cheap, and easily inserted implant for general use in conditions of poor aftercare (Christie, Singh).

These seven working sessions were complemented by the tremendous hospitality of our Japanese hosts, although those unable or unwilling to use chopsticks failed to benefit to the greatest extent.

Robert C. Drews was elected president to take office on January 1, 1981, and Drs. Hayano and Epstein were elected to the Honorary Life Membership by acclamation; they join a small and illustrious group consisting of Ridley, Binkhorst, and the like.

After the meeting several members were taken into the Peoples' Republic of China by Jerre Minor Freeman for a ten-day tour of hospital ophthalmic units in Shanghai and Peking, which was a great success.

The next major meeting of the International Intra-Ocular Implant Club will take place in San Francisco at the time of the next International Congress of Ophthalmology; in the meantime there will be smaller but significant meetings with the Dutch Intraocular Implant Club (April 27-29, 1979) in Rotterdam, followed by a meeting with the French Implant Society in Cannes (May 3-5, 1979). In April 1980 there will be a joint meeting with the United Kingdom Intra-ocular Implant Society in conjunction with the European Congress of Ophthalmology.

A. E. A. RIDGWAY

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CONTINUING OPHTHALMIC MEDICAL EDUCATION

In December 1977, Allergan Pharmaceuticals, Inc., surveyed ophthalmologists to learn their attitudes about continuing medical education (CME). Bill Isaacs, Group Marketing Director of Allergan, and Bert Winograd, an independent marketing consultant, recently shared the survey's findings with THE JOURNAL. The results indicated a widespread frustration concerning various aspects of continuing education. At the outset, it should be noted that ophthalmologists purchase more medical and ophthalmic books than any other specialty group; the number of new ophthalmic titles published annually is exceptionally large.

The Allergan respondents averaged more than an hour a day in continuing medical education activities. Considering the plethora of journals, educational releases from manufacturers, and similar material that arrives daily, this is not surprising. We combine reading of journals and books, listening to tape cassettes with attending conferences and meetings. Our Academy pioneered in providing instruction courses in addition to the annual scientific program. A glance through the advertising pages of THE JOURNAL indicates hundreds of ophthalmologists teaching and thousands attending special courses. The five-year cumulative index lists over 300 books reviewed in THE JOURNAL between 1973 and 1977. Ophthalmologists are indeed a studious group.

Then what are the causes of dissatisfaction with continuing medical education? The ophthalmic clinician interested in providing the best possible care to his patients has specialized in delicate surgery and exact medical diagnosis, yet there is no credit for continuing medical education unless the specific experience is verified and documented. There is no way the scholar can receive credit for retiring to his study to learn all he can concerning a particular disorder or the management of a specific patient. He may spend hours reading textbooks and standard journals, and thus become an expert in a particular aspect of ophthalmology, but credit is not

available. Indeed, we are all frustrated by not knowing exactly what credits are.

Educational credits originated with the American Medical Association and its Physicians Recognition Award (PRA). They are divided into categories from 1 to 5. Category 1 credits are awarded by institutions varying from hospitals to universities to medical societies. Categories 2 through 5 are awarded for activities that involve mainly individual effort. Most licensing groups recognize only Category 1 credits.

Many physicians responding to the Allergan questionnaire resented excessive fees for conferences. High tuition combined with travel costs, housing, and the loss of practice income makes away-from-home instruction extremely expensive. It is, however, possible to fulfill most state relicensure requirements through various, inexpensive methods available for use in the office or at home. One cannot escape though the costs required to maintain permanent records, provide educational objectives, interpret results, provide pre-tests and post-tests and tabulate credits.

Ophthalmologists who responded to the Allergan survey strongly resent the mandatory aspects of the continuing education program. Many fear that they have devoted their lives to developing skills in a particular aspect of ophthalmology only to find themselves being tested about unrelated topics. This resentment is understandable because ophthalmologists maintain skills in the areas for which they accept responsibility. There may be the rare individual who doesn't keep abreast of current information unless prodded by threats of loss of recertification. I suspect, however, that such practitioners limit themselves in practice to doing what they know best, and that they do not pose a threat to life and limb, as our legislators might have us believe.

Stross and Harlan[1] of the University of Michigan reviewed the impact of compulsory mandatory continuing medical education after the first re-registration cycle and compared the results to those of a similar survey of Michigan physicians performed in 1970 before implementation of the Michigan law. They emphasized the undeveloped nature of the CME system and the need for research into learning how a practicing physician learns. They emphasized that CME must be evaluated as to its effect on the practice of medicine. The mere cataloging of hours of attendance at meetings has no importance if the care provided to patients does not improve.

As indicated by the growing number of states passing relicensure laws, mandatory continuing medical education is with us permanently. Whether or not it will improve medical practice depends upon methods of evaluation that are either not available or have not been studied. Nonetheless, the CME movement is gaining momentum. The wise ophthalmologist will make certain that those activities providing CME credit are properly verified. Additionally, he will be certain that he is not wasting time on activities labelled educational, which offer credit without increasing knowledge or skill.

FRANK W. NEWELL

REFERENCE

1. Stross, J. K., and Harlan, W. R.: The impact of mandatory continuing medical education. J.A.M.A. 239:2663, 1978.

CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper, with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

Aniridia, Cataracts, and Wilms Tumor

Editor:

The article, "Aniridia, cataracts and Wilms tumor in monozygous twins,"

(Am. J. Ophthalmol. 1978) 86:129, by Cotlier, Rose and Moel, is important for several reasons. Most obviously, these monozygous twins are discordant for the development of an overt Wilms tumor, which is an important factor to those trying to understand the basis for development of Wilms tumor in at-risk individuals. We have recently published data,[1] providing a chromosomal basis for at least some individuals that have aniridia, genitourinary anomalies, and mental retardation (AGR triad) and are thus known to be at risk for the Wilms tumor. In an addendum to that article we made reference to a pair of twins known to have the AGR triad, including one with a Wilms tumor. Those twins are the twins discussed in the article by Cotlier, Rose, and Moel. Our chromosome analyses show that both of the twins have identical deletions of the short arm of chromosome 11, with break points at 11p12 and 11p15.1. A partial karyotype for each of the twins demonstrates this interstitial deletion (Figure). These twins and their relevant cytogenetic and gene marker data are the subjects of a separate report. The purposes of this communication are twofold:

1. To make certain that readers of THE JOURNAL understand that the twins reported by Cotlier, Rose, and Moel, contrary to their statements about normal chromosomes, do indeed have a deletion of the short arm of chromosome 11. This is important in view of the recent widespread interest in the association of this relatively consistent chromosome abnormality in patients with the aniridia-Wilms tumor association.

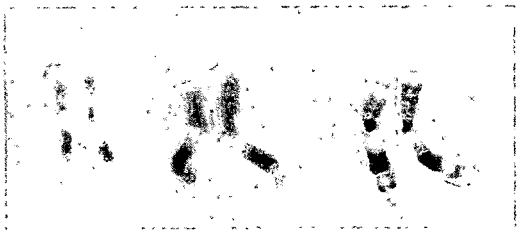


Figure (Ricchardi and Borges). In each chromosome 11 pair, the del(11p) is on the reader's left.

2. To point out that chromosome analyses done using inadequate techniques can be disastrously misleading, especially in instances where we are trying to sort out the cause and pathogenetic mechanisms for embryonal tumors. We urge that all instances of aniridia, particularly if associated with other anomalies, with or without the Wilms tumor, be studied by the newer sophisticated chromosome analysis techniques.

We thus share the enthusiasm of Dr. Cotlier and his associates for elaborating on details about these children. Additionally, we wish to clarify that their chromosome constitutions do indeed include del(11p).

VINCENT M. RICCARDI, M.D.
Houston, Texas
WAYNE BORGES, M.D.
Chicago, Illinois

REFERENCE

1. Riccardi, V. M., and associates: Chromosomal imbalance in the aniridia-Wilms tumor association. 11p Interstitial deletion. Pediatrics 61:604, 1978.

Reply

Editor:

Drs. Riccardi and Borges' chromosomal studies on the twins, which we reported in our paper, revealed a deletion of chromosome 11; thus, providing a solid basis for the genetic abnormality in this syndrome. We are most thankful for this update on the clinical study conducted in 1974 at the University of Illinois Eye and Ear Infirmary, Chicago, Illinois.

A nonbanded chromosome analysis conducted before 1974 at Children's Memorial Hospital, Chicago, and a banded chromosome analysis at a commercial laboratory had been interpreted as normal. Two of the three cases reported by Riccardi and associates[1] also had previ-

ous chromosome analysis which were reported as normals. The awareness of 11p interstitial deletion in the aniridia-Wilms' tumor syndrome should encourage detailed chromosome studies in these patients.

EDWARD COTLIER
New Haven, Connecticut

Color Defective Individuals

Editor:

I wish to comment on the letter by S. Pearl, "Color defective individuals" (Am. J. Ophthalmol. 85:722, 1978).

I would like to stress two important points that were not brought out by Drs. Pokorny and Smith in their reply to Dr. Pearls' letter. Dr. Pearl had encountered a "red color-blind" patient, who apparently had some rectal bleeding that Dr. Pearl concluded the patient failed to realize because of the patient's "color-blindness."

The first important point is that this patient was not really "red color-blind." It was not that the patient did not see the blood in his stool, but that he did not recognize it as being red in color. As he states in his letter, the patient, "realized in retrospect that there had been 'a peculiar color change' in the customary brown color with which he was familiar." Thus in actuality this patient was aware of a change in color of his stools, and despite being "color-blind" he still could have reported the color change, no matter what color it was. We often think that "color-blind individuals" are "blind" to the various colors involved, but almost always these colors are perceived by them, but excite a different sensation than in other so-called "normal individuals."

The final point I wish to emphasize is that color screening should be performed routinely at least in all male children at the time of their first eye examination if they are old enough to cooperate; or at their next annual or biannual examination until this is completed. It is inexcusable for this individual to learn of his color vision proficiency at the time of applying for entrance to a military academy, or to take a test to become an airline pilot, fireman, or the like. The test with either the Ishihara or H-R-R plates is simple and easily performed by a physician himself or a trained assistant. The H-R-R plates are preferred since blue-yellow deficiencies can also be detected in addition to red-green.

JOEL PORTER, M.D.
Daly City, California

Adult Metachromatic Leukodystrophy

Editor:

I was interested to see the report "The ultrastructure of the retina in adult metachromatic leukodystrophy" (Am. J. Ophthalmol. 85:841, 1978), by H. Goebel, K. Shimokawa, A. Argyrakis, and H. Pitz. However, the authors in their introduction state that, to their knowledge, their report represents the first account of the ultrastructure of the retina in adult metachromatic leukodystrophy. Richard Green and I reported the clinical and ultrastructual ocular histopathologic studies of adult-onset metachromatic leukodystrophy in which not only ultrastructure of the retina, but also of the optic nerve were reported along with clinical studies of the patient during life and including fluorescein angiography and electroretinography.[1]

It was interesting to us that Goebel and associates found as we did that there was no metachromasia by light microscopic histochemistry in the retina, whereas the optic nerve did show extensive metachromasia. Although they found a few ganglion cells involved by abnormal inclusions, their histochemistry suggests that the major abnormality, which would have

been interesting to examine ultrastructurally, was in the optic nerve. Apparently, they did not embed or examine the optic nerve by electron microscopy. This is surprising because their case appears to have had ocular involvement at an earlier stage than our case and because the pathogenesis of the lesion in metachromatic leukodystrophy, both in their work and as suggested in our Discussion, is optic nerve degeneration with secondary descending atrophy back to the ganglion cell body. An early case, such as theirs, would tell us somewhat more about the early optic nerve disease than did a more extensively atrophied pair of nerves, as in our case.

HARRY A. QUIGLEY, M.D.
Baltimore, Maryland

REFERENCE

1. Quigley, H. A., and Green, W. R.: Clinical and ultrastructural ocular histopathologic studies of adult-onset metachromatic leukodystrophy. Am. J. Ophthalmol. 82:472, 1978.

Reply

Editor:

We appreciate the comments by Dr. Quigley and must admit that we missed their important paper of the fine structural changes in the eye in adult metachromatic leukodystrophy. However, in contrast to their not finding abnormal residual bodies in ganglion cells in their female patient, we were able to document these in our patient's retinal ganglion cells. Contrary to their statement that our case represents ocular involvement at an earlier stage than their case, our patient had mild ophthalmoscopic changes only shortly before death, which occurred when she was 46 years old, whereas Quigley's patient died at the age of 25 years. This difference in age at the time of death may reflect the presence of residual bodies in retinal ganglion cells of our patient but not in corresponding ganglion cells of their patient. We apparently agree that two factors may be responsible for the accumulation of abnormal residual bodies in retinal ganglion cells in metachromatic leukodystrophy, namely myelin disease of the optic nerve and abnormal storage substances in ganglion cell bodies as a contributing element as they deemed possible but could not substantiate,[1] while they found such ganglionic inclusions in addition to pathologic metachromasia in the optic nerve.

With respect to the optic nerve, our aim was to study the ultrastructure of the retina in adult metachromatic leukodystrophy, firstly, to compare it with reports on the fine structure of the retina in infantile metachromatic leukodystrophy which had also shown considerable clinical and histologic involvement; and secondly, to study the retina as a nonmyelinated gray matter organ in a disease that primarily affects myelin metabolism. Therefore, incorporation of optic nerve histopathology and its metachromasia only served to document fully the type of the disease rather than presenting a detailed study on the ultrastructure of the optic nerve changes. Since, for electron microscopy, we embedded optic nerve as well as other areas of central nervous system white matter for comparative studies, the fine-structural disease of the optic nerve in this patient will be reported separately in association with the ultrastructural disease of other white matter regions of this patient, especially as we expected the optic nerve ultrapathology to be more related to the white matter ultrapathology than to the gray matter retina disease. These studies are currently in progress.

HANS H. GOEBEL, M.D.
Göottingen, West Germany

BOOK REVIEWS

Are Enough Physicians of the Right Types Trained in the United States? Report to The Congress of the United

States by the Comptroller General. U. S. General Accounting Office, Distribution Section, Room 4522, 441 G St., NW, Washington, DC 20548, 1978. $1

In 1963, the United States Congress enacted the Health Professionals Educational Assistance Act (Public Law 88-129) and established the first federal program directed at meeting critical needs for physicians and certain other professional health manpower. It provided financial assistance to schools for construction of facilities and assistance to students in the form of loans. The scope of this legislation was subsequently broadened, and in 1971, the comprehensive health manpower training act specifically provided for special project grants to determine the geographic and specialty distribution of physicians and other health profession personnel. Thus in fiscal year 1977, 578 million dollars was authorized and 409 million dollars was appropriated mainly to medical schools and students in the form of construction assistance, capitation grants, special powers, projects, student loans and scholarships, and health manpower education initiative awards. In light of this appropriation the General Accounting Office (GAO) addressed the questions of whether the numbers of various types of physicians are appropriate to the needs of the country. The answer was sought from the Coordinating Council on Medical Education together with its constituent agencies, the Department of Health, Education, and Welfare, Veterans Administration, the Department of Defense, and the Federal Trade Commission. Additionally, the opinion of residency review committees, specialty boards, specialty societies, and subspecialty societies, was sought together with the views of directors of graduate medical training programs. The GAO recommended that the Department of Health, Education, and Welfare, through its Graduate Medical Education National Advisory Committee, make the necessary study. (Bruce E. Spivey, M.D., president of the Pacific Medical Center, San Francisco, and executive vice-president of the American Academy of Ophthalmology, serves as a member of this committee.) Additionally, they recommended a collection and analysis of the following data: morbidity and mortality information; number and type of patients seeking physician care in various specialties; number, ages, and geographic location of practicing physicians by specialty and subspecialty; number and types of procedures actually performed by physicians in various subspecialities; the ways various specialists interrelate; number of physician extenders and other types of paraprofessionals entering the medical field and the duties they perform; likely imminent changes in the various specialties because of technological breakthroughs; and reimbursement mechanisms, possible changes thereto, and their impact on physician specialty choices.

After completion of these studies, the GAO recommends that the Department of Health, Education, and Welfare and the Council of Coordinating Medical Societies reach some mutual agreement on approximate manpower supply and requirements, in order to provide a reasonable assessment of the nation's present and future needs for the various types of physicians and physician extenders. The GAO abandoned its initial proposal that the accreditation process be used as a means for seeing that appropriate types and numbers of physicians were trained in each type of specialty. Additionally, they abandoned the proposal that the Coordinating Council on Medical Education be the primary group concerned with the collection and analysis of data regarding the supply of physicians.

In this day of concern regarding restraint of trade, as we witness the end of the California relative fee schedule, and challenges to anesthesiology and radiolo-

gy specialty societies, the comments of the Federal Trade Commission concerning the report prepared by the General Accounting office are scholarly and germane. The Bureau of Competition, a litigating unit of the Federal Trade Commission, has already submitted to the United States Office of Education its opinion that the Liaison Committee on Medical Education should not be the accreditating agency for medical schools. Pending is administrative litigation involving the American Medical Association, one of the five sponsors of the Coordinating Council on Medical Education.

The directors of the Bureau of Competition and the Bureau of Economics stated that although the GAO Report assumes a national need for physician services, which can be accurately measured and to which a supply of physicians can be matched, it does not define "national need," a term they state is ambiguous without further explanation. The directors state that there are various indicia of need relative to various social goals of resource allocation: equity, happiness, physical survival, and many others, the goals of which must be identified before methods of achieving them can be analyzed. Moreover, the effort to measure future need requires the future to be forecast, which always involves uncertainty or changes in conditions that were the basis of the estimates of the needed manpower which would render the target numbers inadequate.

According to this comment, the report deals with complex social and economic problems and makes recommendations that will have serious consequences. The report, however, does not evaluate critical assumptions and issues.

The report thus provides an interesting exchange between two powerful sections of government, one interested in fostering competition; the other interested in controlling costs through limiting supply. It makes interesting reading for believers and nonbelievers that the future can be found in the clouded crystal of the past.

FRANK W. NEWELL

Structures of Ocular Vessels. By Kaichi Shimizu and Kazuyoshi Ujii. New York, New York, Igaku-Shoin, 1978. Hardcover, 144 pages, forward, table of contents, index, 110 black and white figures, 2 color figures. $39

This is an extraordinary book, or rather, an atlas of a special kind. By injecting a low viscosity plastic monomer into the carotid arteries of macaques and subsequently digesting away the soft tissues of the eyes, the authors have obtained beautiful polymer casts of the ocular vessels. These are then examined by three dimensional electron microscopy and illustrated in the text by 112 black and white photographs that are scientifically and esthetically breathtaking.

Although, as the authors point out, the specimens reproduce only the luminal angio-architecture and are subject to some inevitable artifacts, they provide valuable correlation with results obtained by fluorescein angiography, india ink injections, and trypsin digestion techniques. Nowhere else in the body has such a precise correlation of appearances during life, pathology of removed tissue and electron microscopy been possible as in the case of ocular vessels. This atlas presents a complete reproduction of the inner walls of the ocular vessels (retinal, uveal, nerve head, conjunctival, and palpebral) including such details as the impressions of the endothelial nuclei and of the microvilli. Some of the preparations may be viewed in three dimensions and some are presented as both front and rear views.

The average clinician may feel this atlas tells him more than he really wants to know about the anatomic details of a

monkey's ocular vasculature but he cannot help but be thrilled by this demonstration of its organization. Moreover, he should realize that what has been shown for the monkey's vessel applies to those of man. Investigators, both those within and outside of ophthalmology, concerned with vascular mechanisms will find the book a vade mecum of angio-architecture. The description of the technique and the results presented serve as a model for further studies and those of us interested in both clinical and pathological studies will look forward eagerly to exploitation of the technique to ocular angiopathology.

DAVID G. COGAN

Scientific Foundations of Ophthalmology. Edited by Edward S. Perkins and David W. Hill. Chicago, Year Book Medical Publishers, Inc., 1977. Clothbound, 337 pages, table of contents, 178 black and white figures, 35 tables.

Lives there an ophthalmologist who in the past year or two has not said to himself, "I really must brush up on my immunology" (for immunology substitute freely from the following list: ultrastructure, physiology, biochemistry, genetics, endocrinology, metabolic disease). This apparently random listing is actually the content of the first five sections of this book and might be considered a review of the basic sciences as they apply to ophthalmology. A section on epidemiology follows and the remainder of the text is then devoted to the physiology of vision and some of its pathologic alterations.

Generally each section consists of four or five topics and as might be expected from a compendium such as this the approach by the different authors varies. In some cases the topic is narrow and exhaustive, for example, gyrate atrophy and hyperornithemia. Conversely, in the same general section is a rather broad-ranging discussion of genetics in clinical medicine, which in a few short pages refreshes the mind and directs one to a series of useful basic texts in medical genetics.

Other broader treatments that are particularly enjoyable (the bias of this reviewer of this type of presentation is apparent) are the introduction to epidemiology by Nizetic, a review of the morphology of the retinal receptors and pigment epithelium by J. Marshall, and a discussion of the visual pigments by Kemp.

The clinical chapters are on the whole much less appealing and rewarding. Much of the material in these sections can be found in standard texts and journals and is not really in the category of basic science. For example, the surgery of strabismus can hardly be called a scientific foundation of ophthalmology. The same cavil applies to treatment of serous detachment of the central retina, a well-done essay but hardly in the category of basic science. However, this is a small objection and on balance the merits of this book far outweigh the defects. The short presentations make nice reading on a rainy Sunday afternoon after you've finished the New York Times crossword.

DAVID SHOCH

SYMPOSIA

Symposium on Strabismus. Edited by Eugene M. Helveston, Arthur Jampolsky, Philip Knapp, Keith W. McNeer, Marshall M. Parks, Robert D. Reinecke, William E. Scott, and Gunter K. von Noorden. St. Louis, C. V. Mosby, 1978. Hardcover, 608 pages, index, 419 black and white figures. $45.50

GUNTER K. VON NOORDEN: **Ambloypia. Basic concepts and current treatment**

KURT SIMONS AND ROBERT D. REINECKE: **Amblyopia screening and stereopsis**

GUNTER K. VON NOORDEN: Present status of sensory testing in strabismus

WILLIAM E. SCOTT: Clinical study of saccadic eye movements

KEITH W. MCNEER: Histopathology of extraocular muscles in strabismus

WILLIAM E. SCOTT: Office use of prisms

ARTHUR JAMPOLSKY: Spring-back balance test in strabismus surgery

EUGENE M. HELVESTON: Sutures and needles for strabismus surgery

WILLIAM E. SCOTT: Differential diagnosis of vertical muscle palsies

EUGENE M. HELVESTON: Surgery of the superior oblique muscle

MARSHALL M. PARKS: Surgery for Brown's syndrome

MARSHALL M. PARKS: Surgical approach to the extraocular muscles

KEITH W. MCNEER: Adulthood and childhood strabismus

KEITH W. MCNEER: Childhood and adulthood strabismus surgery

ROBERT D. REINECKE: Recess-resect operation

EUGENE M. HELVESTON, JAMES H. PATTERSON, FORREST D. ELLIS, AND JANET C. WEBER: En-bloc recession of the medical recti for concomitant esotropia

ARTHUR JAMPOLSKY: Surgical leashes and reverse lashes in strabismus surgical management

MARSHALL M. PARKS: Causes of the adhesive syndrome

ROBERT D. REINECKE AND MUHIB TARAKJI: Adhesive strabismus syndrome (ciatricial strabismus): surgical results

PHILIP KNAPP: Blow-out fractures

KEITH W. MCNEER: Complications of strabismus surgery

PHILIP KNAPP: Lost muscle

GUNTER K. VON NOORDEN: Posterior fixation suture in strabismus surgery

ARTHUR JAMPOLSKY: Adjustable strabismus surgical procedures

PHILIP KNAPP: Paretic squints

ARTHUR JAMPOLSKY: Unequal visual inputs and strabismus management: a comparison of human and animal strabismus

WILLIAM E. SCOTT: Sensory testing: examination techniques

ROBERT D. REINECKE: Neurological aspects of strabismus

GUNTER K. VON NOORDEN: Esotropia

ARTHUR JAMPOLSKY: Exotropia

KEITH W. MCNEER: A-V syndrome

Advances in Ophthalmology, vol. 37. Ophthalmic Microsurgery. Edited by S. S. Ratnam, B. C. Ang, I. Constable, C. Y. Khoo, A. S. M. Lim, and C. F. Tham. Basel, Switzerland, S. Karger, 1978. Clothbound, 232 pages, table of contents, 80 black and white figures, 19 tables. $64. 25

MISHIMA, S., AND TAKIZAWA, S. (*Tokyo*): Development in microscope designs

BEALE, J. P., JR. (*San Francisco*): Microsurgery using the stereovideo microscope

IBRAHIM, S. (*Padang*): An inexpensive operation microscope made from two common binoculars

PATKIN, M. (*Whyalla*):Selection and care of microsurgical instruments

VICKERS, D. W. (*Brisbane*): Design of microsurgical instruments

ANDERSON, B. M. (*Noble Park, Australia*): Design, structure and care of microinstruments

SUTHERLAND, G. (*Melbourne*): Instruments for intraocular microsurgery

GIRARD, L. J.; NIEVES, R., AND HAWKINS, R. S. (*Houston*): The Girard ultrasonic fragmentor

CLEASBY, G. W. (*San Francisco*): The Klöti vitreous stripper

PATKIN, (*Whyalla*): Ergonomics and the operating microscope

LIM, A. S. M.; KHOO, C. Y., AND ANG, B. C. (*Singapore*): Practical microsurgery

HOWSAM, K. G. (*Melbourne*): Training of registrars with the operating microscope

HEINZE, J. (*Melbourne*): Microsurgery and the lacrimal system

KALEVAR, V. (*Ahmedabad*): Suturing in corneal grafting

SABISTON, D. (*Napier*): Keratoconus and the operating microscope

MOORE, T. E., JR., AND ARONSON, S. B. (*San Francisco*): Results of penetrating keratoplasty in keratoconus

MAGUIRE, C. J. F. (*Belfast*): Suturing techniques in corneal surgical incisions and traumatic lacerations

SLADE, J. H. (*Adelaide*): Cataract wound suturing with the operating microscope

ROBERTSON, I. F. (*Melbourne*): Postoperative astigmatism and the operating microscope

STROW, W. F. (*Springfield, Illinois*): Computer analysis of 637 patients done with loupe and 102 patients done with microscope

GIRARD, L. J. (*Houston*): Ultrasonic fragmentation for cataract extraction and cataract complications

MAGUIRE, C. J. F. (*Belfast*): Combined simultaneous cataract glaucoma surgery

CONSTABLE, I., AND LIM, A. S. M. (*Perth*): Intraocular lens implants

LANDERS, J. A. G. (*Adelaide*): A current perspective on intraocular lens implantation

LANDERS, J. A. G. (*Adelaide*): Some technical aspects of intraocular lens implantation

ROBERTSON, I. F. (*Melbourne*): Continuous-wear hydrophylic contact lenses versus intraocular lenses

SLADE, J. H. (*Adelaide*): Secondary intra-ocular lens implants—ten years' experience

BEALE, J. P., JR. (*San Francisco*): Microsurgical correction of optical errors refractive keratoplasty and intraocular lenses

CONSTABLE, I. (*Perth*): Vitreous microsurgery

WATSON, P. G. (*Cambridge*): Microsurgery in glaucoma

WILLIS, R. (*Malvern, Australia*): The office use of the microscope in otology

WILLIS, R. (*Malvern, Australia*): The choice and care of instruments for oto-microsurgery

KHOO, J. C. M. (*Singapore*): The microsurgery of brain tumours

STOKES, B. A. R. (*West Perth*): The operating microscope in the treatment of intracranial aneurysms

AMACHER, L. (*London, Ontario*): The microsurgical anatomy of lumbar rachischisis

LEONG, H. S. (*Singapore*): Replanted upper limbs in Singapore: A report of the first two cases

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

Albrecht von Graefes Archiv für Klinische und Experimentelle Ophthalmologie

ROLE OF DEBRIDEMENT AND INTERFERON IN THE TREATMENT OF DENDRITIC KERATITIS. Sundmacher, R., Cantell, K., Haug, P., and Neumann-Haefelin, D. (Univ. Eye Clinic, Freiburg, West Germany). Albrecht von Graefes Arch. Klin. Ophthalmol. 207:77, 1978.

In a controlled clinical study, 42 patients with dendritic keratitis were treated either with thermocautery plus human leukocyte interferon (HLI) or with minimal wiping debridement plus HLI. The results show that the efficiency with which primary debridement was carried out determined the success of further therapy using interferon. The authors conclude that interferon works basically as a prophylactic agent and needs the support of further antiviral measures to be effective against dendritic keratitis. (3 figures, 2 tables, 7 references)—Authors' abstract

Archives of Internal Medicine

ENDOPHTHALMITIS FOLLOWING STAPHYLOCOCCAL SEPSIS IN RENAL FAILURE PATIENTS. Bloomfield, S. E., David, D. S., Cheigh, J. S., Kim, Y., White, R. P., Stenzel, K. H., and Rubin, A. L. (New York Hosp.- Cornell Med. Ctr., New York, N.Y.). Arch. Intern. Med. 138: 706. 1978.

Endophthalmitis occurred three months following completion of therapy for documented staphylococcal septicemia in two patients on long-term hemodialysis. The indolent course of the endophthalmitis, and its excellent response to systemic and subconjuntival antibiotics and subconjunctival and topical corticosteroid therapy, suggest the possibility that the acute fulminating clinical course of metastatic bacterial endophthalmitis may be modified in this population of patients. The reason for this modified clinical picture is probably the immune incompetence associated with uremia, which favors both the development of metastatic endophthalmitis as well as altering its clinical presentation. While funduscopic examination is suggested in all dialysis patients with eye complaints, this procedure becomes mandatory following episodes of sepsis. (3 figures, 17 references)—Authors' abstract

Archives of Ophthalmology

CLINICAL EVALUATION OF THE 6600 AUTOREFRACTOR. Pappas, C. J., Anderson, D. R., and Briese, F. W. (Bascom Palmer Eye Inst., Univ. of Miami School of Med., Miami, Fla.). Arch. Ophthalmol. 96:993, 1978.

The 6600 Autorefractor was evaluated on 200 patients undergoing refraction. The automatic refractor showed a high degree of accuracy in determining the needed refractive correction, but the errors are sufficient that the automatic refractor alone without subjective refinement cannot be substituted for conventional complete refracting methods with subjective refinement. However, for aphakic patients and for patients with clear media and cylindric corrections over 0.50 diopters, the automatic refractor can be used as a substitute for retinoscopy in determining the starting point for a subjective refraction. (1 figure, 4 tables, 14 references)—Authors, abstract

IS THE AUTOREFRACTOR READING CLOSEST TO MANIFEST REFRACTION? Pap-

pas, C. J., Anderson, D. R., and Briese, F. W. (Bascom Palmer Eye Inst., Univ. of Miami School of Med., Miami, Fla.). Arch. Ophthamol. 96:997, 1978.

In a study of 56 patients, the old glasses of a previously refracted individual were as close to the final subjective refraction as the reading obtained with a 6600 Autorefractor. Therefore, the previous spectacle correction might logically be used for the starting point of a subjective refraction with retinoscopy or automatic refractor results being used for this purpose in patients whose previous spectacle refraction is unknown or in the first refraction of an aphakic patient. (1 table, 7 references)—Authors' abstract

British Journal of Ophthalmology

A NEW SYSTEM OF MICROSURGERY FOR HUMAN AND EXPERIMENTAL CORNEAL GRAFTING. I. THE CONTACT LENS CORNEAL CUTTER, STEREOTAXIC EYE HOLDER, DONOR DISK CHUCK, AND FRAME. II. CLINICAL AND EXPERIMENTAL APPLICATIONS. Crock, G. W., Pericic, L., Rajendran, B., Chapman-Smith, J. S., Carroll, N., Maclean, H., and Scrimgeour, J. (Royal Victorian Eye and Ear Hosp., Melbourne, Australia). Br. J. Ophthalmol. 62:74 and 81, 1978.

The cutting instrument and accessories described in these two papers are the end result of a five-year experimental program designed primarily to perfect the technique of deep, nonpenetrating corneal grafting (down to the level of Descemet's membrane). The cutter is hand-held and hand-operated; it is funnel-shaped, with its lower end closed off by a quartz contact lens, designed to fit and to brace the cornea of the donor eye. The disposable cutting blade has a single cutting point which projects beyond the undersurface of the contact lens by a variable and precisely controllable amount. The cutting is done by rotation of the blade in a circular brace, the motion being actuated and visually controlled by the surgeon. The new instrument comes in three sizes (7, 8 and 9 mm) and is described as being equally useful in the operating room, in the morgue and in a private residence. In the latter two situations the donor eye is "reconstructed" with a haptic contact lens. The ease and precision of the procedure has "transformed" the task of donor collection. Permission for the collection can now be sought on less emotive terms and without the need of far-reaching legal reforms. The new microsurgical system has improved and, at the same time, simplified existing techniques of penetrating keratoplasty. The second paper describes the operative routine in detail and gives the visual results in 25 cases. (22 figures, 1 table, 19 references)—Peter C. Kronfeld

Diabetologia

HLA PHENOTYPES AND DIABETIC RETINOPATHY. Moller, E., Persson, B., and Sterky, G. (St. Goran's Childrens' Hosp., Stockholm, Sweden). Diabetologia 14:155, 1978.

The incidence of HLA antigens B8, BW15, DW3 and DW4 was found to be significantly increased in 99 patients with growth onset, insulin-dependent diabetes of more than 15 years duration. Different degrees of retinopathy were seen in 75% of the patients. No significant correlation between the presence of specific HLA alleles and the stage of retinopathy was found. It is possible that all patients who develop diabetes have identical disease-predisposing genes, irrespective of their HLA alleles. If this is the case, the HLA pheontype would not determine the risk of developing diabetic retinopathy. (2 tables, 19 references)—Authors' abstract

Investigative Ophthalmology

THE EFFECT OF PREDNISOLONE ON ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXOCITY AND THE GROWTH OF TYPE I HERPES SIMPLEX VIRUS IN HUMAN CELLS. Cooper, J. A., Jr., Daniels, C. A., and Trofatter, K. F., Jr. (Dept. Pathol., Duke Univ. Med.

Ctr., Durham, N. C.). Invest. Ophthalmol. 17:381, 1978.

Treatment of human skin and corneal fibroblasts with prednisolone-21-phosphate did not increase the capacity of these cells to replicate type I herpes simplex virus (HSV). The corticosteroid however was found to inhibit human lymphocytes from mediating antibody-dependent cell-mediated cytotoxicity (ADCC) against HSV-infected fibroblasts and to suppress the replication of virus in PHA-stimulated human lymphocytes. The data suggest that the exacerbation observed when patients with dendritic keratitis are inadvertently treated with prednisolone may be due to the corticosteroid suppressing ADCC and not by promoting the growth of virus in the corneal cells. (1 figure, 2 tables, 11 references)—Authors' abstract

EFFECT OF DARK-REARING ON EXPERIMENTAL MYOPIA IN MONKEYS. Raviola, E., and Wiesel, T. N. (Dept. Anat., Harvard Med. School, Boston, Mass.). Invest. Ophthalmol. 17:485, 1978.

When lids are surgically fused in rhesus monkeys before eye growth is completed, a high degree of myopia develops, which is caused by an elongation of the eye globe. The present study shows that in monkeys raised in the dark after monocular lid fusion, refraction and axial length were normal in both the closed and the open eye. Myopia, however, readily developed and the eye elongated when a monkey raised in the dark was transferred to illuminated quarters. These findings indicate that visual stimulation through the translucent lids was necessary for the development of this experimental ametropia. (1 figure, 13 references)—Authors' abstract

Klinische Monatsblätter für Augenheilkunde

APPLANATION TONOMETRY IN MEDICAL DIAGNOSTIC CHECKUP PROGRAMS. (German) Ruprecht, K. W., Wulle, K. G., and Christl, H. L. (Wiesbaden, West Germany). Klin. Monatsbl. Augenheilkd. 172: 332, 1978.

Applanation tonometry intraocular pressure (IOP) measurements were performed on 8,899 patients seen in a general medical diagnostic clinic. The IOP did not have a Gaussian distribution but was skewed to the right with an excess of higher pressures. There was a small, almost linear increase of IOP with age. The mean pressure (n = 17,709 eyes) was 16.2 mm Hg. Also, 2.18% of the men and 1.81% of the women had IOP greater than 21 mm Hg.; 0.66% of the men and 0.58% of the women had an IOP greater than 24 mm Hg. Of all patients 40 years old and older, 4.92% of the men and 4.88% of the women had IOP greater than 21 mm Hg. Of patients 55 years old and older, 5.75% of the men and 6.69% of the women had IOP greater than 21 mm Hg. (3 tables, 5 figures, 23 references)—Peter Egbert

INVESTIGATION OF OBJECTIVE PERSONALITY TRAITS IN PATIENTS WITH CENTRAL SEROUS RETINOPATHY. (German) Wery, H., and Arends, C. (Eye Clinic, Hannover Med. School, Hannover, West Germany). Klin. Monatsbl. Augenheilkd. 172:363, 1978.

Central serous retinopathy has been associated with certain personality types. In order to prove and define these personality types, the Minnesota Multiphasic Personality Inventory (MMPI) was administered to 33 persons with angiographically-proven central serous retinopathy and 33 age-and sex-matched control subjects. The subjects with retinopathy showed a tendency to hypochondriasis, depression and the development of hysteria and conversion reactions. (1 table, 6 figures, 35 references)—Peter Egbert

Metabolic Ophthalmology

CORTICOSTEROID GLAUCOMA. François, J. (Univ. of Ghent, Ghent, Belgium). Metabolic Ophthalmol. 2:3, 1978.

Chronic as well as acute glaucoma can be induced by corticosteroids. The hypertensive response to the topical corticosteroid test is not genetically determined. The pathogenesis of the corticosteroid glaucoma can be explained by clones of goniocytes, which contain mucopolysaccharides sensitive to hyaluronidase.

When these mucopolysaccharides are polymerized, they retain water and when they are depolymerized, they lose water. As the corticosteroids strengthen the lysosomal membranes, the retained catabolizing enzymes prevent the catabolism of the mucopolysaccharides, which tend to accumulate in a more polymerized and more hydrophilic form. (8 figures, 3 tables, 32 references)—Author's abstract

PAPILLEDEMA IN BASSEN-KORNZWEIG SYNDROME. Manor, R. S., and Berrebi, A. (Beilinson, Med. Ctr., Petah Tikva, Israel). Metabolic Ophthalmol. 2:45, 1978.

The Bassen-Kornzweig syndrome is a very rare hereditary disease. Its biochemical pattern is characterized by an absence of serum betalipoprotein and very low levels of serum alpha-1-lipoprotein, cholesterol, phospholipids and triglycerides. This abnormal plasma environment is responsible for the pathological changes produced in erythrocytes, visual cells, nervous system and the small intestine. A woman harboring the signs of Bassen-Kornzweig syndrome was followed by the authors for 11 years. A benign intracranial hypertension with bilateral papilledema appeared under puzzling circumstances: second month of pregnancy, daily medication with vitamin A and an influenza-like illness. The possibility that this benign intracranial hypertension was provoked by hypervitaminosis A should be kept in mind when administering high doses of vitamin A in patients with Bassen-Kornzweig syndrome. (10 figures, 20 references)—Authors' abstract

New England Journal of Medicine

A RANDOMIZED TRIAL OF ASPIRIN AND SULFINPYRAZONE IN THREATENED STROKE. Barnett, H. J. M. - Canadian Cooperative Study Group (Dept. Neurological Sciences, Univ. Hosp., London). N. Engl. J. Med. 299:53, 1978.

Five hundred and eighty-five patients with threatened stroke were followed in a randomized clinical trial for an average of 26 months to determine whether aspirin or sulfinpyrazone, singly or in combination, influence the subsequent occurrence of continuing transient ischemic attacks, stroke, or death. Eighty-five subjects went on to stroke, and 42 died. Aspirin reduced the risk of continuing ischemic attacks, stroke, or death by 19% ($P < .05$) and also reduced risk for the "harder," more important events of stroke or death by 30% ($P < .05$), but this effect was sex-dependent; among men, the risk reduction for stroke or death was 48% ($P < .005$), whereas no significant trend was observed among women. For sulfinpyrazone, no risk reduction of ischemic attacks was observed, and the 10% risk reduction of stroke or death was not statistically significant. No overall synergism or antagonism was observed between the two drugs. The authors conclude that aspirin is an efficacious drug for men with threatened stroke. (1 figure, 5 tables, 22 references)—Authors' abstract

Ophthalmic Surgery

CLINICAL ASPECTS OF THE VISUALLY EVOKED POTENTIAL. Weinstein, G. W. (Univ. of Texas Health Science Ctr., San Antonio, Tex.). Ophthalmic Surg. 9:56, 1978.

The visually evoked potential (VEP) was studied in normal and abnormal human subjects, and in rhesus monkeys. A relatively simple protocol for clinical VEP testing is described. The monkeys showed similar but smaller VEP responses compared to those obtained from human subjects. Central, but no paracentral or peripheral photocoagulation retinal lesions were associated with VEP abnormalities. The second, smaller wave of the response complex to 10 Hz flash stimuli corresponds to the primary evoked response, and is closely related to visual acuity. It was possible to recognize visually this VEP waveform and subjectively interpret the record correctly in 85% of eyes with regard to visual acuity. Therefore, the clinican can "read" the VEP record in response to non-patterned flash stimuli. This test was further validated in a series of patients with opacities of the ocular media. VEP promises to become a procedure of diag-

nostic and prognostic value in ophthalmology. (6 figures, 1 table, 23 references)—Author's abstract

Ophthalmology

PARS PLANA VITRECTOMY FOR THE MANAGEMENT OF SEVERE DIABETIC RETINOPATHY. Blankenship, G. W., and Machemer, R. (Bascom Palmer Eye Inst., Univ. of Miami School of Med., Miami, Fla.). Ophthalmol. 85:553, 1978.

Fifty-six eyes with advanced complications of proliferative diabetic retinopathy and marked loss of vision had pars plana vitrectomies. After five years of follow-up, 17 patients had died, three eyes had been removed for neovascular glaucoma, and two patients were lost to follow-up. Of the 34 eyes available for examination five years after surgery, approximately 50% had regained or retained sufficient vision for independent ambulation, with 15% having 6/12 (20/40) or better visual acuity. The anatomic findings showed a clearing of the vitreous cavities sufficient to allow examination of the macula in 58% of the eyes and the macula to be attached in at least 50% of the eyes. None of the eyes showed development of new neovascular proliferation. Most of the visual and anatomic improvement was obtained during the first six months after surgery. (6 tables, 3 references)—Authors' abstract

A LOGICAL APPROACH TO THE TREATMENT OF MASSIVE PERIRETINAL PROLIFERATION. Machemer, R., and Laqua, H. (Bascom Palmer Eye Inst., Univ. of Miami School of Med., Miami, Fla.). Ophthalmol. 85:584, 1978.

Based on the improved understanding of massive periretinal proliferation as a proliferative membrane-forming disease, a new therapeutic approach is presented with the technique of pars plana vitreous surgery. Not only vitreous membranes but also preretinal membranes are removed. Forty-seven consecutive patients who suffered from severe massive periretinal proliferation were operated on with this technique and followed for six months or more. Seventeen patients (36%) had an attached retina. Twelve patients had a major visual improvement. The major postoperative complication was phthisis bulbi, found in ten eyes (21%). (2 figures, 2 tables, 16 references)—Authors' abstract

Pediatrics

INFECTIONS AND OTHER MATERNAL FACTORS AS RISK INDICATORS FOR CONGENITAL MALFORMATIONS: A CASE-CONTROL STUDY WITH PAIRED SERUM SAMPLES. Koskimies, O., Lapinleimu, K., and Saxén, L. (Children's Hosp., Helsinki, Finland). Pediatrics 61:832, 1978.

An obstetric population of 48,000 individuals was prospectively followed up for evidence of possible teratogenic factors that might be associated with congenital malformations. Serum samples from 274 mothers of defective children and from paired controls were collected during early pregnancy and approximately one month after delivery and tested for antibodies against ten different viruses, *Mycoplasma pneumoniae*, and *Toxoplasma*. These data were supplemented with clinical information on infections, other diseases, drug intake, and other potentially teratogenic factors during pregnancy. Mothers of defective children had more seroconversions (fourfold or greater increase in titer) than the controls, 123 vs. 86. This difference was mainly due to an increase in herpes simplex viruses 1 and 2, cytomegalovirus, varicella-zoster virus, and *Toxoplasma* titers. In addition, the number of reported diseases during the pregnancy, the intake of drugs (especially analgesics and hormones), and the number of earlier abortions were greater in the mothers of the defective children than in the controls. (6 tables, 14 references)—Authors' abstract

Survey of Ophthalmology

THE MANAGEMENT OF SMALL CHOROIDAL MELANOMAS. Char, D. H. (Ocular

Oncology Unit, Univ. of California, San Francisco, Calif.) Surv. Ophthalmol. 22:377, 1978.

Clinicopathologic studies suggest that patients with small choroidal melanomas (less than 10 mm in diameter and 3 mm in height) have an excellent prognosis. In patients with small choroidal melanomas with clear ocular media and no clinical retinal detachment, it is reasonable to do serial examinations without therapeutic intervention until growth is documented. In patients with small choroidal melanomas in which growth is documented, enucleation or alternate modes of therapy, including photocoagulation or radiation, are reasonable methods of treatment. (68 references)—Author's abstract

Vision Research

POLARIZED LIGHT RETINAL PHOTOGRAPHY OF A MONKEY EYE. Hochheimer, B. F. (Johns Hopkins Univ., Laurel, Md.). Vision Res. 18:19, 1978.

Polarized light photographs have been taken of a monkey retina at discrete wavelengths from 400 to 830 nm. These photographs show a cross-like figure overlying the macular area. Because of the position and shape of this cross it is probably due to the same structure in the eye that produces the Haidinger's brushes phenomenon. This polarization figure is attributed to effects arising from the dichroism of Henle's layer. (2 figures, 1 table, 15 references)—Author's abstract

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.

700 North Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least three months before the date of occurrence.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE: POSTGRADUATE COURSE

The Annual Postgraduate Course presented by the American Association for the Study of Headache will present its annual postgraduate course, "Diagnosis and Treatment of Headache," Jan. 12-14, 1979, at the Registry Resort in Scottsdale, Arizona. Registration fee is $200. For further information, write Robert S. Kunkel, M.D., Vice President and Course Director, The Clinic Center, 9500 Euclid Ave. Cleveland, OH 44106.

NEW ORLEANS ACADEMY OF OPHTHALMOLOGY: 28TH ANNUAL SYMPOSIUM

The New Orleans Academy of Ophthalmology will hold its 28th Annual Symposium on Medical and Surgical Diseases of the Cornea March 31-April 4, 1978, at the Hyatt Regency, New Orleans. The registration fee is $250 for practicing ophthalmologists; $75 for residents outside of Louisiana (with a letter from the Chief of Service). For further information, write Paula D. Stephens, Executive Secretary, New Orleans Academy of Ophthalmology, 931 Canal St., Suite 517, New Orleans, LA 70112; telephone (504) 561-1085.

NEW YORK MEDICAL COLLEGE: VITRECTOMY SYMPOSIUM

The New York Medical College, Department of Ophthalmology will sponsor a Vitrectomy Symposium at the Barbizon Plaza Hotel, Nov. 17-18, 1978. For further information, write Danny H. Kaufman, M.D., One Stone Place, Bronxville, NY 10708.

ROYAL AUSTRALASIAN COLLEGE OF SURGEONS: SECOND MICROSURGICAL WORKSHOP

The Second Microsurgical Workshop, sponsored by the Royal Australasian College of Surgeons, will be held in Singapore Dec. 4-10, 1978. The workshop is designed for surgeons who have never used the operating microscope or who are having adjustment difficulties. For further information, write Arthur S. M. Lim, M.D., Chairman, Workshop on Microsurgery, 441 Singapore Medical Center, Tanglin Shopping Center, 19 Tanglin Road, Singapore 10.

COLORADO OPHTHALMOLOGICAL SOCIETY: MIDWINTER MEETING

The Eighth Annual Midwinter Meeting of the Colorado Ophthalmological Society will be held Feb. 3-7, 1979, at the Steamboat Village Inn, Steamboat Springs, Colorado. For further information, write William E. Smith, M.D., Program Chairman, Colorado Ophthalmological Society, 1601 E. 19th Ave., Denver, CO 80218.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO: POSTGRADUATE COURSE ON CORNEAL AND EXTERNAL DISEASES

The University of California, San Francisco, will hold a postgraduate course, and "Corneal and External Diseases," Feb. 15 and 16, 1979, in San Francisco. For further information, write Extended Programs in Medical Education, University of California, Room 569-U, Third and Parnassus Avenue, San Francisco, CA 94143; telephone (415) 666-4251.

NEW ORLEANS OPHTHALMIC MICROSURGERY SEMINAR

The Fourth Annual New Orleans Spring Fiesta Ophthalmic Microsurgery Seminar will be held May 3-5, 1979. The subject of the seminar will be cataract surgery and intraocular lens implantation. For further information, write Azar Foundation, 144 Elk Place, Suite 1501, New Orleans, LA 70112; telephone (504) 524-6077.

FLORIDA MIDWINTER SEMINAR IN OPHTHALMOLOGY

The Florida Midwinter Seminar in Ophthalmology, "The Cataract Operation," will be held at the Americana Hotel, Miami Beach, Florida, Feb. 5-7, 1979. The seminar is cosponsored by the University of Florida College of Medicine (Gainesville), the University of Miami School of Medicine (Miami), and the University of South Florida College of Medicine (Tampa). Registration fee is $150 for practitioners; $50 for residents upon application from their department head. For further information, write Florida Midwinter Seminar, 405 Northeast 144th St., Miami, FL 33161.

WHITE MEMORIAL MEDICAL CENTER: ALUMNI DAY

White Memorial Medical Center and Loma Linda University Medical School Department of Ophthalmology will hold its Seventh Triennial Alumni Day Feb. 11, 1979, at the White Memorial Medical Center, 414 N. Boyle Ave., Los Angeles, from 8 A.M. to 4 P.M. For further information, write George Kambara, M.D., 414 N. Boyle Ave., Los Angeles, CA 90033.

CLEVELAND CLINIC FOUNDATION: PERSPECTIVES IN OPHTHALMOLOGY

The Department of Ophthalmology of the Cleveland Clinic Foundation will hold a postgraduate seminar, "Perspectives in Ophthalmology," Dec. 7 and 8, 1978. Two half day sessions will be devoted to clinical pathological correlations for the ophthalmic clinician. The other two half day sessions will emphasize ophthalmic plastic surgical problems with symposia on lacrimal surgical problems and thyroid ocular disease. For further information and application forms, write Education Department, Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44106.

NEW JERSEY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY: ANNUAL FALL MEETING

The New Jersey Academy of Ophthalmology and Otolaryngology will hold its Annual Fall Meeting Nov. 15, 1978, at the Town and Campus, West Orange, New Jersey. The topic is cataract. For further information, write Marshall S. Klein, Executive Secretary, c/o Eye Institute of New Jersey, 15 S. 9th St., Newark, NJ 07107.

THE XII SYMPOSIUM NEURORADIOLOGICUM

Giovanni Di Chiro, chief of the Neuroradiology and Computed Tomography Section of the National Institutes of Health, Bethesda, Maryland, has been chosen to be the president of the XII Symposium Neuroradiologicum. The choice, by election, was made at the XI Symposium, recently (June 4-10) held in Wiesbaden, Germany, June 4-10, 1978. The XII Symposium Neuroradiologicum will take place in Washington, D.C., Oct. 10-16, 1982. Vice President of the Symposium is Hillier L. Baker of the Mayo Clinic; secretary general is David O. Davis of the George Washington University Medical Center.

ROYAL AUSTRALIAN COLLEGE OF OPHTHALMOLOGISTS: NEW OFFICERS

The Royal Australian College of Ophthalmologists has announced the following new officers for 1978-1979: E. J. Donaldson, president; G. W. Harley, vice-president; M. Harrison, vice-president elect; F. A. Billson, censor-in-chief; G. Burfitt-Williams, treasurer; and M. D. Steiner, secretary. Robert Ellsworth has been named the Norman McAlister Gregg Lecturer for 1981. The next scientific congress of the college will be held in Sydney, Australia, Oct. 7-12, 1979.

VISION RESEARCH—A NATIONAL PLAN: 1978-1982

The National Advisory Eye Council, senior advisory body of the National Eye Institute (NEI), has released a five-year plan that will serve as a guide in encouraging and supporting research throughout the United States and abroad on blinding and disabling eye diseases.

The research priorities identified in the three-volume report, "Vision Research—A National Plan: 1978-1982," reflect the Council's desire that NEI's program be concentrated in areas of greatest research need and opportunity. The 12 members of the National Advisory Eye Council are appointed by the Secretary of Health, Education, and Welfare to advise the NEI on the development of its policies and programs.

Copies of the report, or any part, are available from the Office of Program Planning and Scientific Reporting, National Eye Institute, Building 31, Room 6A25, National Institutes of Health, Bethsda, MD 20014.

PERSONALS

GUY H. CHAN

Guy H. Chan has been appointed chairman of the Department of Ophthalmology, Temple University Medical Center, Philadelphia.

FREDERICK T. FRAUNFELDER

Frederick T. Fraunfelder has been named chairman of the Department of Ophthalmology of the University of Oregon Health Sciences Center in Portland. Dr. Fraunfelder, is the national director of the Registry of Drug-Induced Ocular Side effects; he was formerly chairman of the Department of Ophthalmology at the University of Arkansas Medical Center in Little Rock.

ROBERT MACHEMER

Robert Machemer has been appointed professor and chairman of the Department of Ophthalmology, Duke University, Durham, North Carolina.

H. SAUL SUGAR

The graduates eye residents of Kresge Eye Institute awarded an educational travel stipend of $500 for 1978-1979 in the name of H. Saul Sugar. The award was made to honor Dr. Sugar for his many years of devoted service to Detroit General Hospital.

New Research Grants Awarded by the National Eye Institute

April 1, 1978 to June 30, 1978

RESEARCH PROJECT GRANTS

Institution	Principal Investigator	Title of Project	Costs Awarded
Carnegie-Mellon University Pittsburgh, Pennsylvania	Terry A. Bahill	Clinical recording of saccades	$ 10,759
University of Pennsylvania Philadelphia, Pennsylvania	Britton Chance	Redox states of normal and pathological corneal conditions	61,277
Swedish Hospital Medical Center Seattle, Washington	John W. Chandler	Herpetic keratitis: Early virus-neuron interactions	38,228
University of Minnesota Austin, Minnesota	Jacques R. Chipault	Lipids of lenticular membranes	46,177
University of Miami Miami, Florida	John G. Clarkson	Branch vein occlusion collaborative study	80,190
State University of Medicine Buffalo, New York	John R. Cotter	Efferent projections from accessory optic nuclei	11,027
Dalhousie University Halifax, Canada	Max S. Cynader	Etiology of strabismus in animals	27,252
Estelle Doheny Eye Foundation Los Angeles, California	Kenneth R. Diddie	Branch vein occlusion collaborative study	36,764
University of Wisconsin Madison, Wisconsin	Sheldon M. Ebenholtz	Determinants of perceptual orientation	26,384
Johns Hopkins University Baltimore, Maryland	Daniel Finkelstein	Branch vein occlusion collaborative study coordinating center	90,614
Johns Hopkins University Baltimore, Maryland	Daniel Finkelstein	Branch vein occlusion collaborative study	53,448
Johns Hopkins University Baltimore, Maryland	Robert W. Flower	Prostaglandins in premature infant vascular physiology	95,446
Johns Hopkins University Baltimore, Maryland	Rudolph M. Franklin	Secretory immune system-relationship to ocular disease	4,613
University of California San Francisco, California	Mitchell H. Friedlaender	Immunopathology of hypersensitivity reactions in the eye	58,913
University of Florida Gainesville, Florida	Kirk N. Gelatt	Congenital cataracts in the miniature schnauzer	48,964
University of California La Jolla, California	Michael H. Goldbaum	Angiogenesis, healing and aging in retina and choroid	56,218
University of Florida Gainesville, Florida	Eugene P. Goldberg	Intraocular lens coatings to prevent cornea damage	54,380
Indiana University Bloomington, Indiana	Henry W. Hofstetter	Indiana University myopia study	28,872
Juntendo University Tokyo, Japan	Izumi, Kabasawa	Aging lens proteins and cataract	18,000

Institution	Principal Investigator	Title of Project	Costs Awarded
University of Michigan Ann Arbor, Michigan	Paul R. Lichter	Carbonic anhydrase inhibitors in treating glaucoma	$105,277
University of Chicago Chicago, Illinois	Frederick A. Mausolf	Experimental hyperviscosity retinopathy	47,007
Eye Research Institute of Retina Boston, Massachusetts	Wallace J. McMeel	Study of retinal circulation in diabetes	84,521
Medical College of Pennsylvania Philadelphia, Pennsylvania	Elizabeth H. Murphy	Development and function of the visual system	148,720
Duke University Durham, North Carolina	Thomas T. Norton	Neural mechanisms of extra-striate and striate vision	59,859
University of Illinois Chicago, Illinois	David H. Orth	Branch vein occlusion collaborative study	52,497
University of Connecticut Farmington, Connecticut	John W. Patterson	Lens fiber formation	54,340
University of Uppsala Uppsala, Sweden	Per A. Peterson	Retinol metabolism with special regard to the eye	53,197
University of Minnesota Minneapolis, Minnesota	Robert C. Ramsay	HLA and genetic studies in diabetic retinopathy	97,761
Virginia Commonwealth University Richmond, Virginia	John J. Ruffolo	Primate ocular photopathology of the lens and retina	91,084
IIT Research Institute Chicago, Illinois	Jon M. Ryan	A study of lens cell division and differentiation	61,752
University of Southern California Los Angeles, California	Stephen J. Ryan	Bruch's membrane/retinal pigment epithelial studies	107,943
University of California San Francisco, California	Julius Schachter	Inclusion conjunctivitis of the newborn	90,448
Medical College of Wisconsin Milwaukee, Wisconsin	Richard O. Schultz	Diabetes mellitus and the anterior segment of the eye	63,888
Wills Eye Hospital Philadelphia, Pennsylvania	Theodore W. Sery	In vitro and in vivo studies of retinoblastoma	64,997
University of Puerto Rico San Juan, Puerto Rico	Susan C. Specht	Axonal transport during visual development	25,215
Eye Research Institute of Retina Boston, Massachusetts	Clement L. Trempe	Branch vein occlusion collaborative study	48,128
University of Illinois Medical Center Chicago, Illinois	Charles M. Vygantas	Diabetic retinopathy in nonhuman primates	71,779

National Research Service Award Fellowship

University of Michigan Ann Arbor, Michigan	Robert M. Loyd	Cell cycle controls in the regenerating lens in vitro	13,000

RESEARCH CAREER DEVELOPMENT AWARDS AND ACADEMIC INVESTIGATOR AWARDS

Institution	Principal Investigator	Title of Project	Costs Awarded
Baylor College of Medicine Houston, Texas	Scott F. Basinger	Photoreceptor pigment epithelium interaction	$37,262
University of Washington Seattle, Washington	Chris R. Kaneko	Premotoneuronal control of fast eye movements	29,766
University of California San Francisco, California	Juan I. Korenbrot	Rhodopsin and transduction in rod photoreceptors	36,196
State University Stony Brook, New York	William G. Owen	Signal transfer between retinal cells	33,293
Eye Research Institute of Retina Boston, Massachusetts	Charles E. Riva	Blood flow and transcapillary exchange in eye fundus	35,347
New York Medical College New York, New York	Sansar C. Sharma	The formation of visual neuronal connections	36,003

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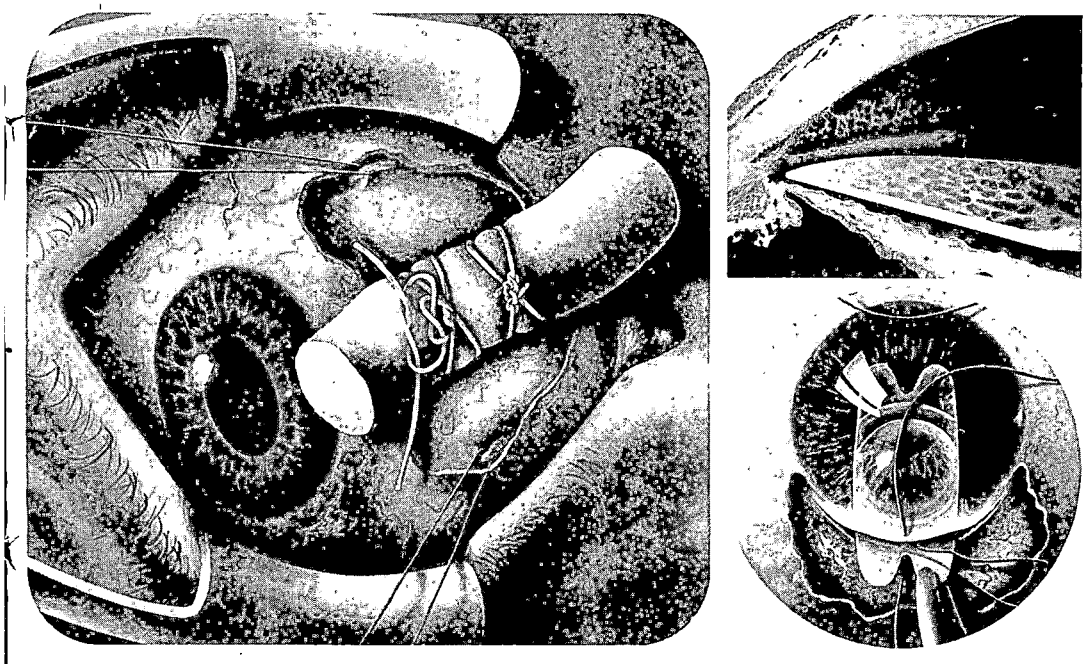
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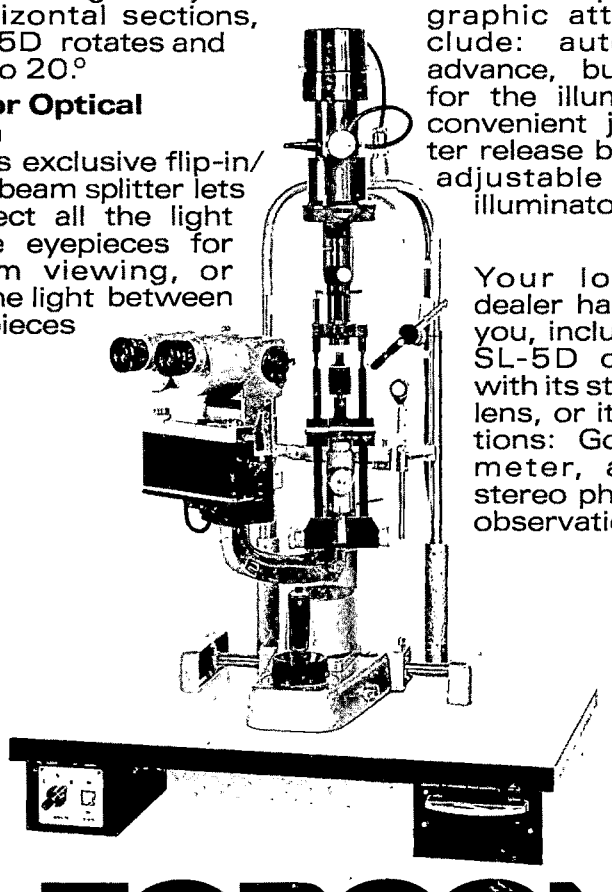
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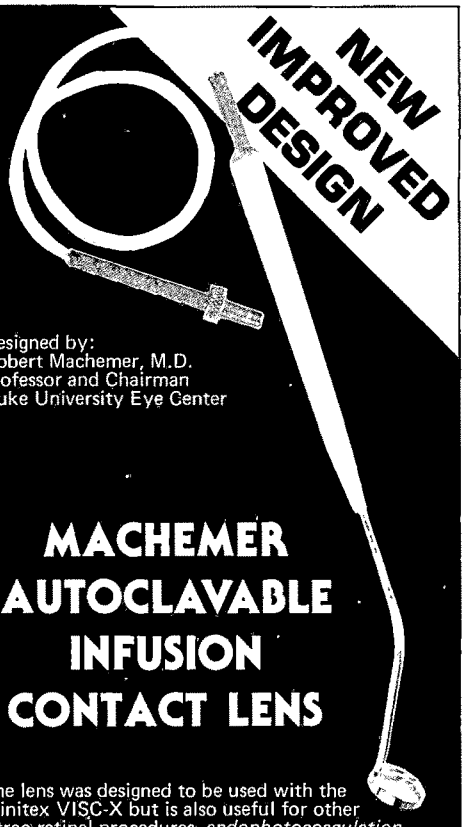
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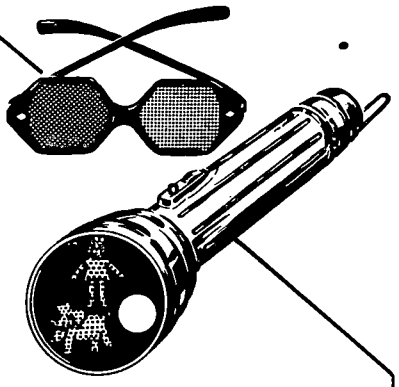
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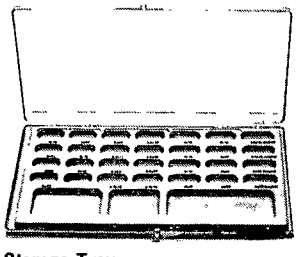
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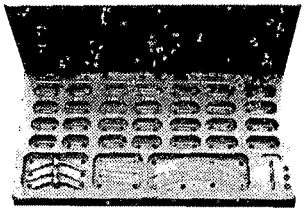
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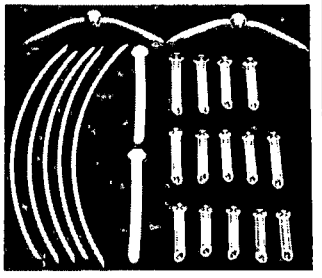
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* L.T. Jones M.D., Dacryocystorhinostomy, American Journal of Ophthalmology, Volume 59, No. 5, May, 1965.
J.C. Mustarde', L.T. Jones M.D. and A. Callahan M.D., Ophthalmic Plastic Surgery---Up-To-Date, Aesculapius Publishing Company, 1970.
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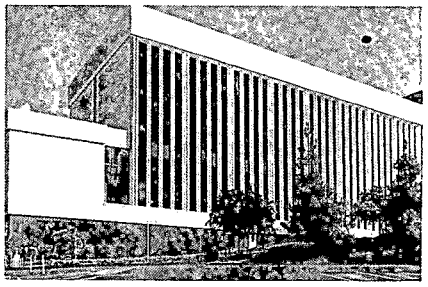
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December 14, 15, 16: 1978

University of Southern California Health Sciences Campus, Los Angeles, California

Ultrasonography—Electrophysiology—Orbital Diagnosis—Office Diagnostic Techniques—Fluorescein Angiography—Oncology/Pathology/Clinicopathologic Correlations

Thursday: Basics A & B Scan, Exam Techniques, Intraocular Diagnosis, Vitrectomy Evaluations, Pre-operative Cataract Evaluation, Intraocular Foreign Bodies, Retinal Physiology, ERG, EOG, VER, Clinical Applications of Electrophysiology, Color Vision Testing, Specular Microscopy, Tear Deficiency, Visual Acuity, Bright Flash

Friday: Radiological Techniques in Orbital Diagnosis, Computerized Tonography, Ultrasound & Doppler in Orbital Diagnosis, Laboratory Diagnosis of Thyroid Disease, Drugs in Ocular Diagnosis, Background, Basics & Perspectives in Fluorescein Angiography, Retinal Vascular Disease, Diabetes, Intraocular Tumors, Iris Angiography, Macular Diseases,

Saturday: Melanotic Epibulbar Lesions & Syndromes, Cornea and Conjunctival Epithelial Tumors, Cytology in Ocular Diagnosis, Iris Tumors, Lid Lesions, Intraocular Melanomas, Oncology and Ocular Melanomas, Lymphoid Tumors, Electron Microscopy, Participating Workshops in Ultrasound, Pathology, Microbiology, Electrophysiology and Photography.

The Estelle Doheny Memorial Lecture
Lorenz E. Zimmerman, M.D.

The A. Ray and Wendell C. Irvine Memorial Lecture
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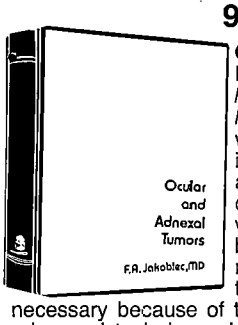
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OCULAR AND ADNEXAL TUMORS: *Frederick A. Jakobiec, M.D.* The author-editor, with the help of the most illustrious ocular tumor authorities and their co-workers have developed an indispensable volume for ophthalmology. This multiauthored approach was necessary because of the explosion of knowledge and techniques in the eye cancer field. Among its outstanding features is the first Algernon B. Reese Lecture by Lorenz E. Zimmerman, M.D., on "The Histogenesis of Conjunctival Melanoma". Section 1 on intraocular melanomas explores the state of the art in diagnosis, natural history, immunology, pathologic concepts, and newly developed conservative managements (cobalt plaques, photocoagulation, proton irradiation, and eye wall resection). New information is presented on the possibility that enucleation can promote tumor metastasis. Section 2 deals with nonmelanomatous intraocular tumors, including the latest facts on retinoblastoma, medulloepithelioma, iris nevus syndrome, hamartomas, and choristomas. Section 3 summarizes the current status of various diagnostic modalities: ^{32}P test, cytology, ultrasonography, electron microscopy, computed tomography, immunology, and enzymology. Section 4 on tumors of the conjunctiva and lids contains new data on sebaceous carinoma and conjunctival carcinoma, lymphoma and melanoma. Several chapters by highly respected authors are offered on radiotherapy and various surgical treatments (including cryotherapy and Mohs' chemosurgery) of lid tumors. Section 5 covers orbital tumors and inflammations and presents the results of many newly completed clinicopathologic series on pediatric orbital tumors, optic nerve gliomas, vascular tumors, pseudotumors, lymphomas and lacrimal gland tumors. Even the statistics are impressive—over 900 pages, 58 chapters with 32 color illustrations and 826 black and white pictures (many with sequences), and 193 tables. Because of the breadth and depth of information provided on clinically important entities, this book is the most authoritative and update reference on the current diagnosis and treatment of tumors of the eye, eyelids, conjunctiva, and orbit. **$100.00**

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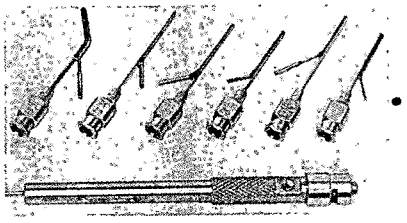
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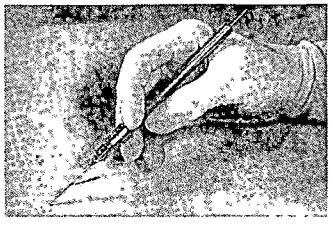
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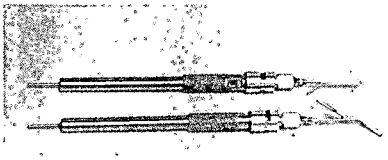
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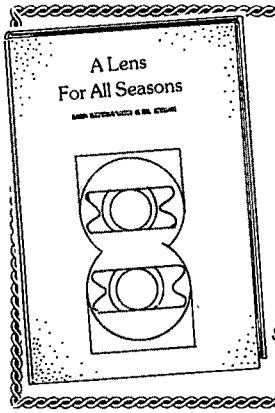
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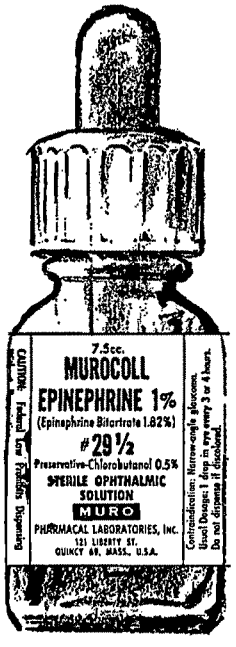
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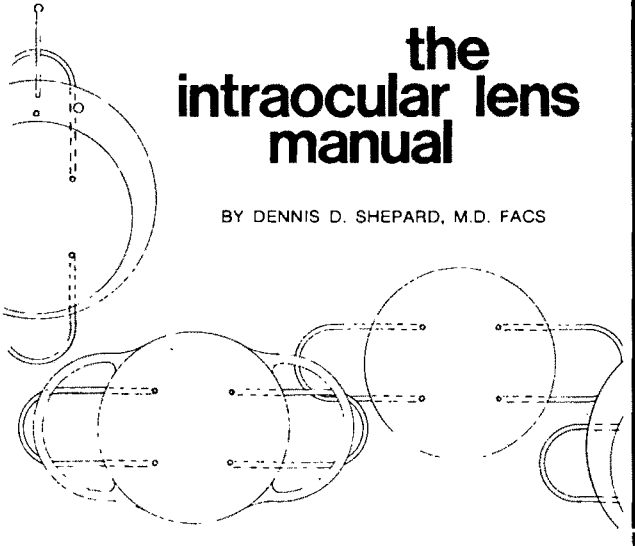
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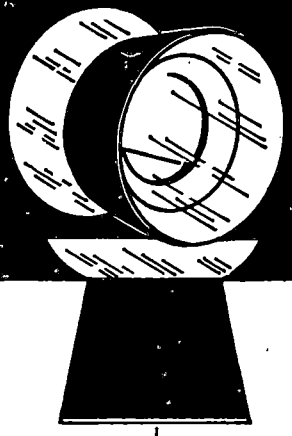
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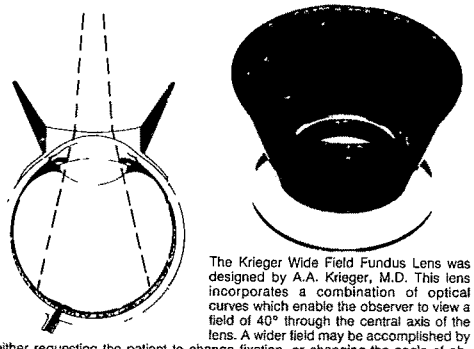
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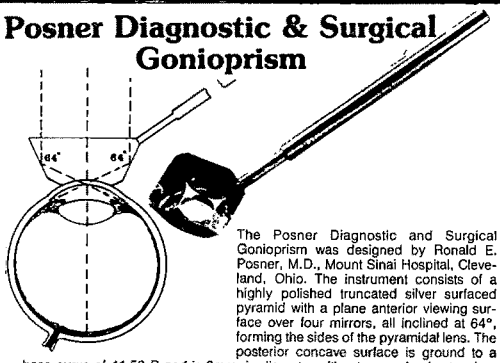
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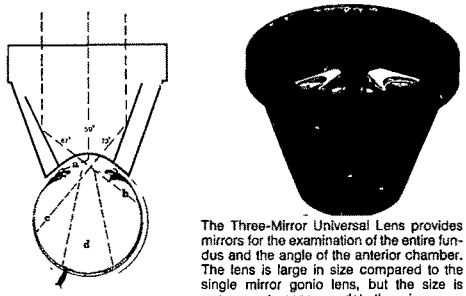
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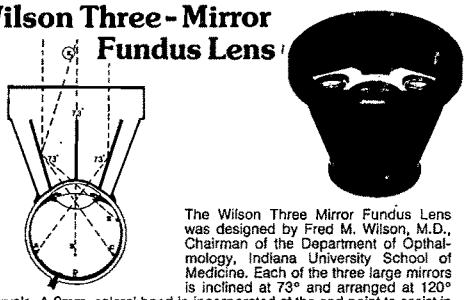
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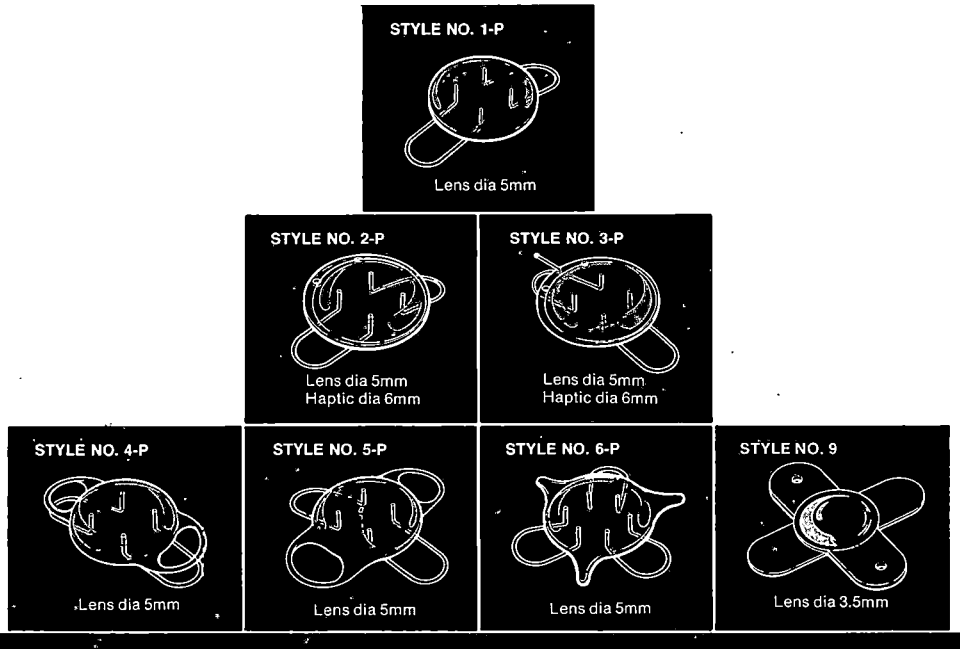
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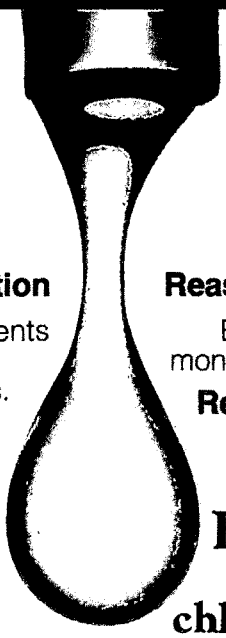
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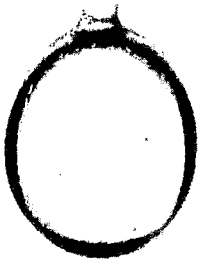
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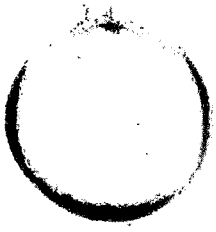
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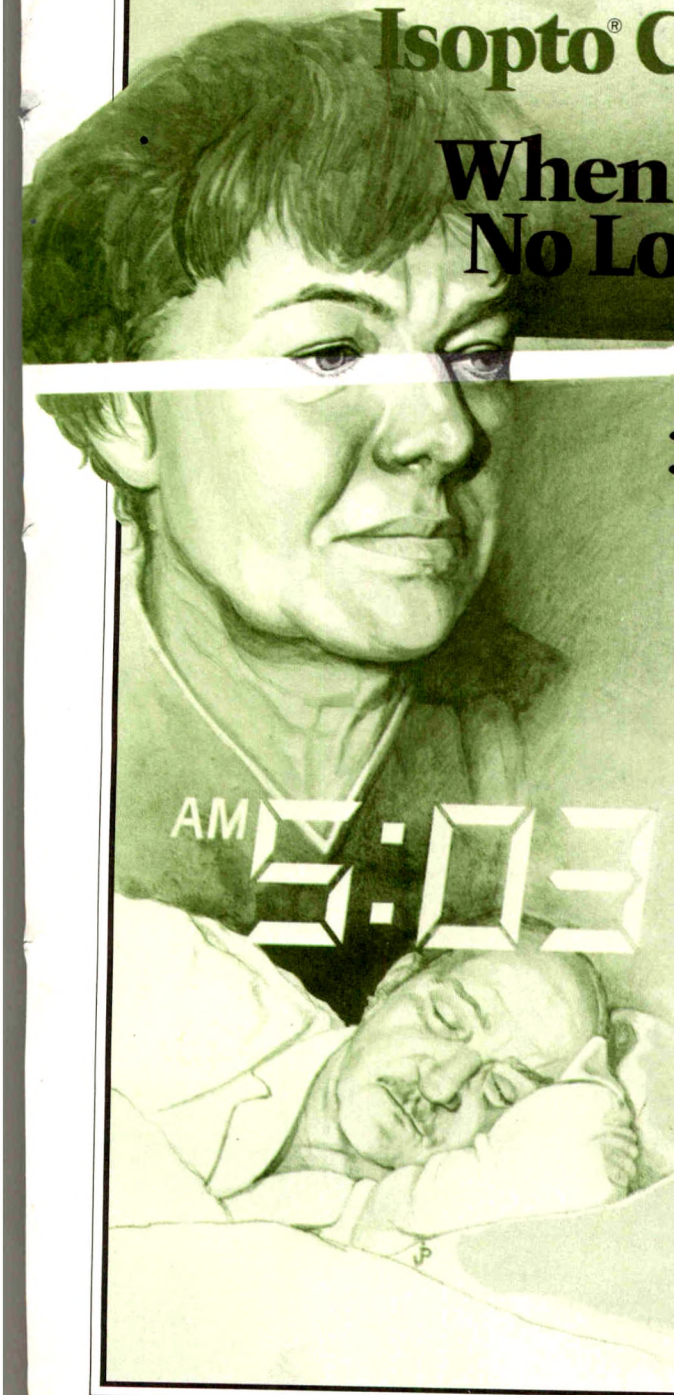
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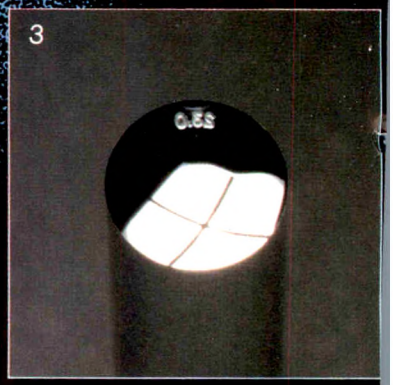
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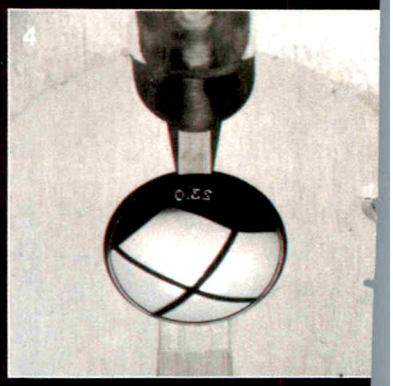


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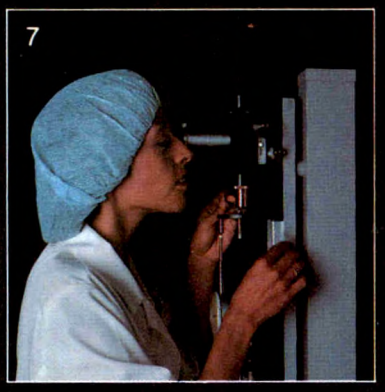
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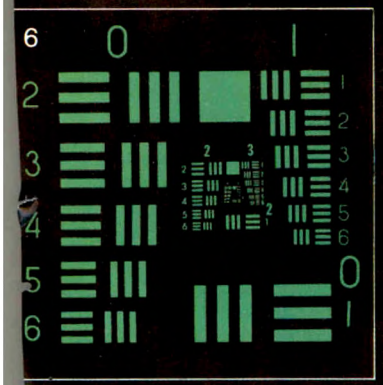
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5 Intraocular lens after molding showing engraved diopter power number.

6 Standard 1951 Air Force target which has been the normal criteria used in precision optics for assessing optical resolution.

7 Quality control inspection in mold department, optical resolution and back focal length are verified with the use of an Auto-Collimator to determine diopter power.

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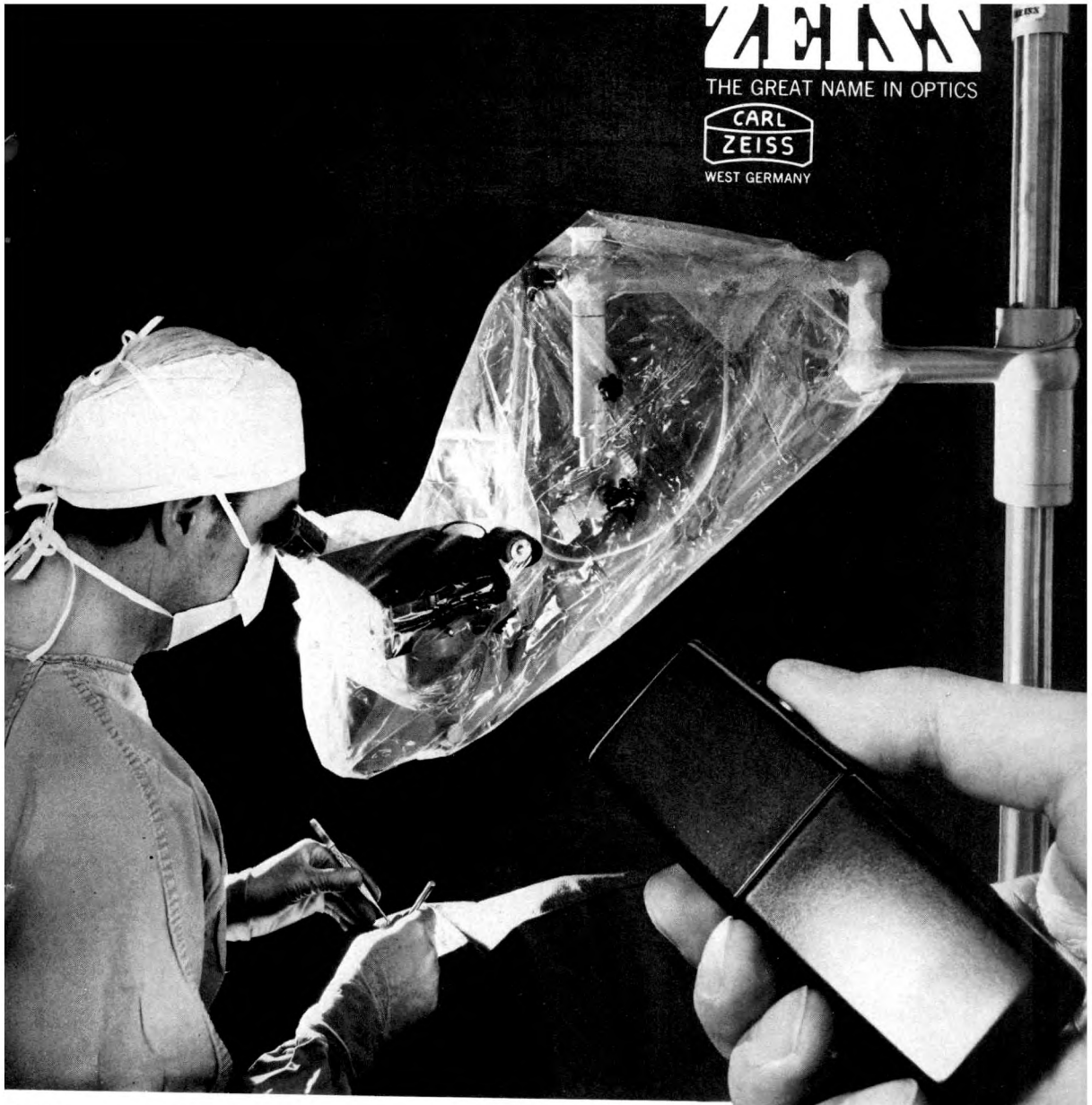
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AMERICAN JOURNAL OF OPHTHALMOLOGY

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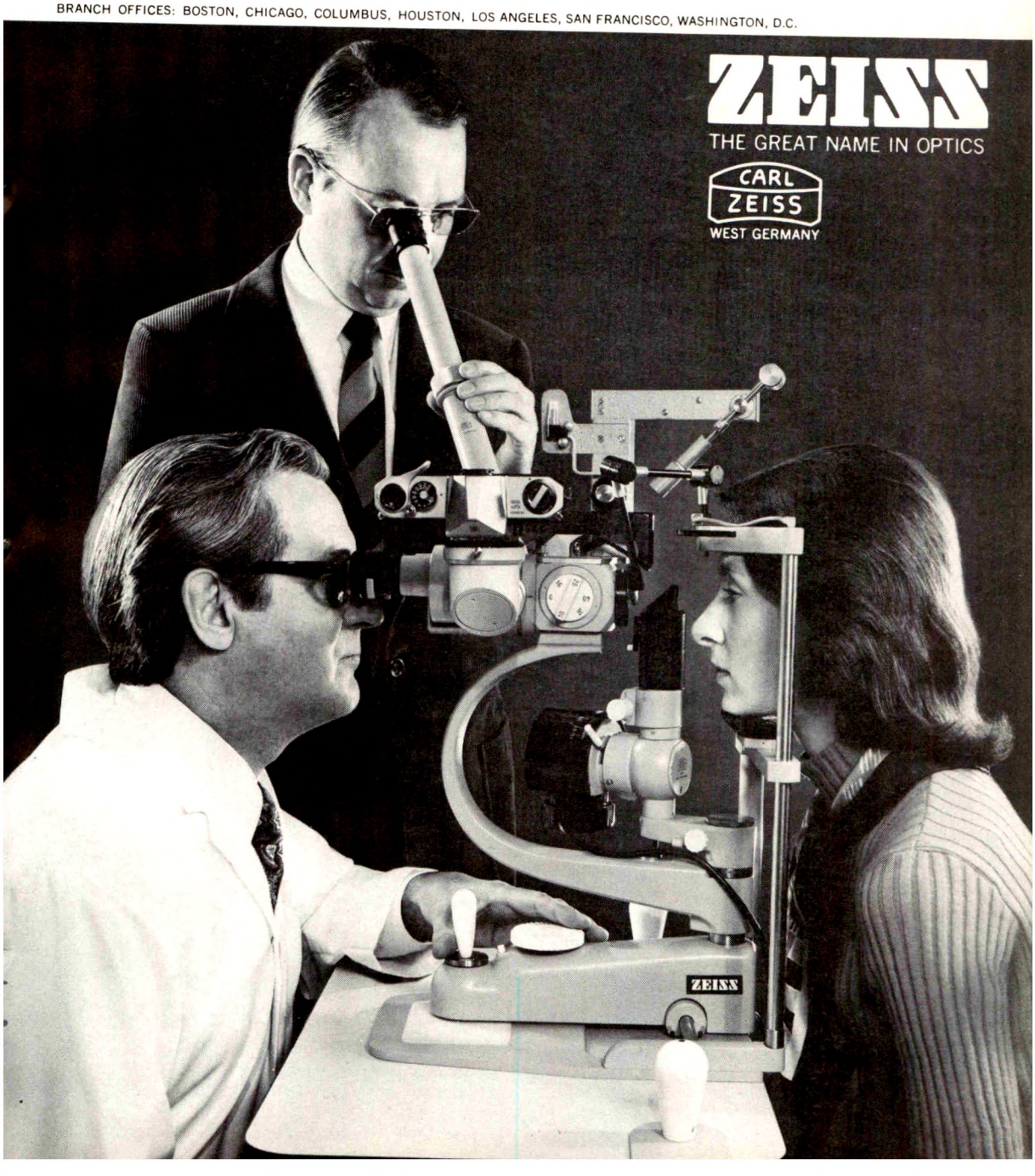
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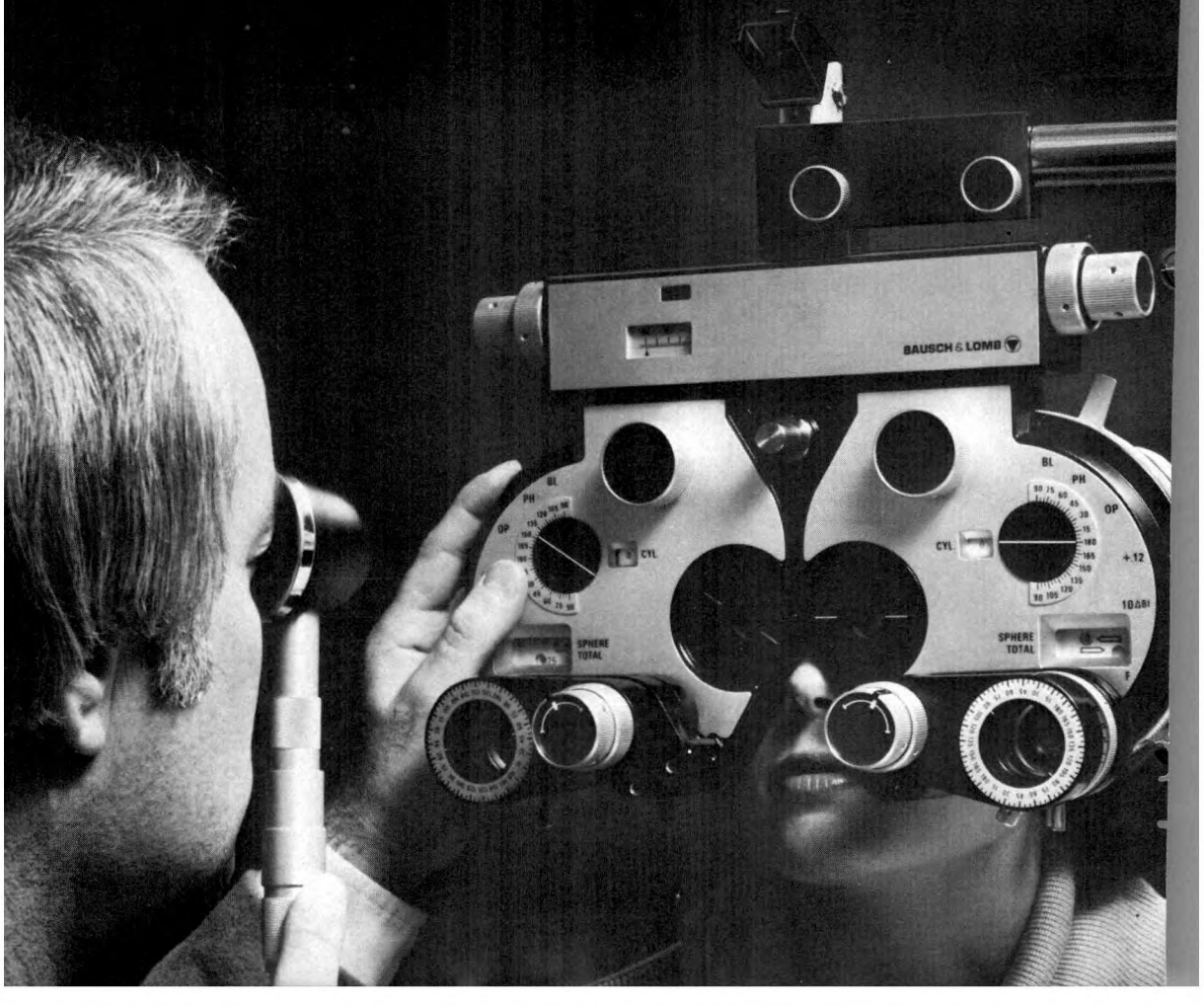
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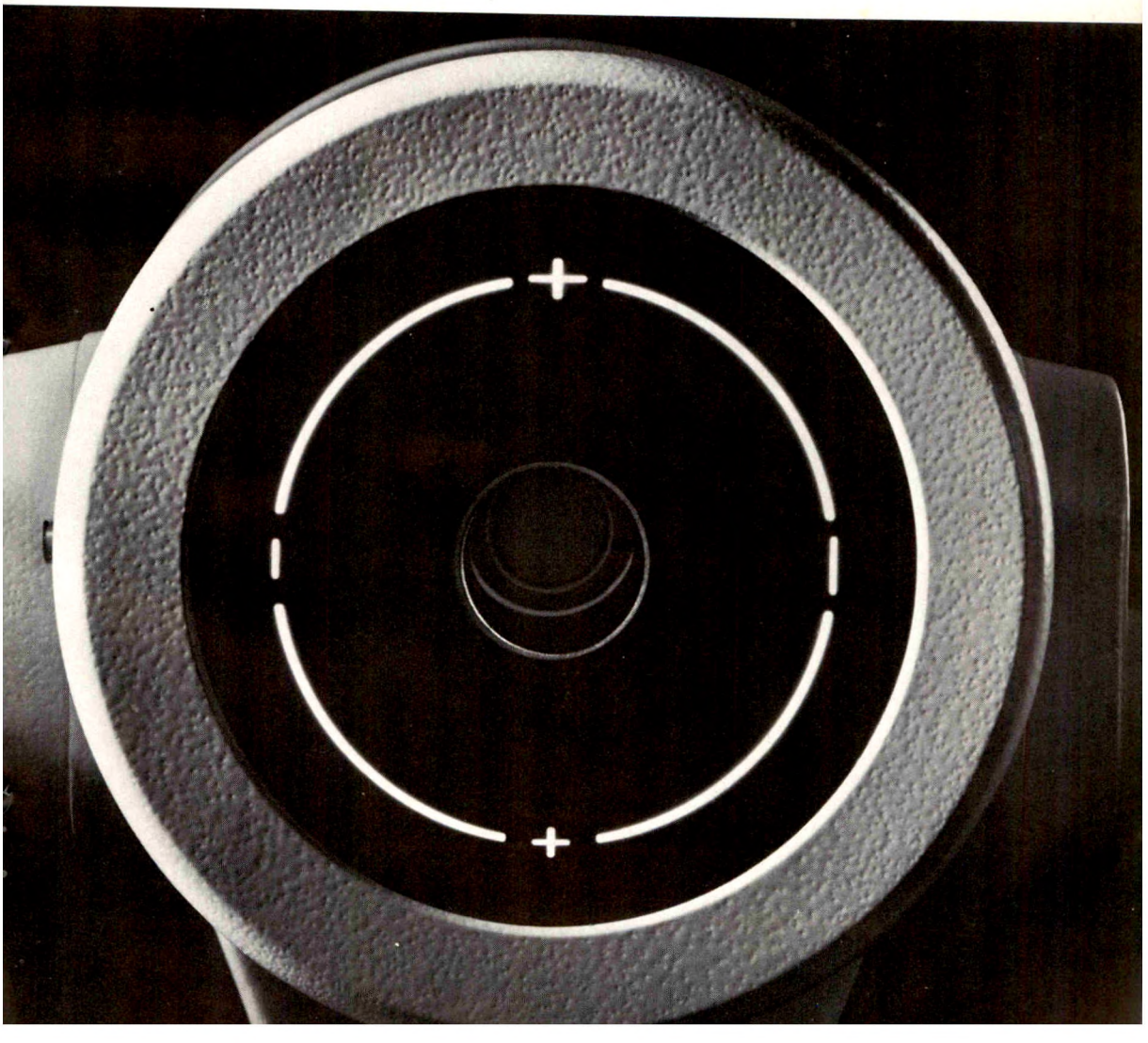


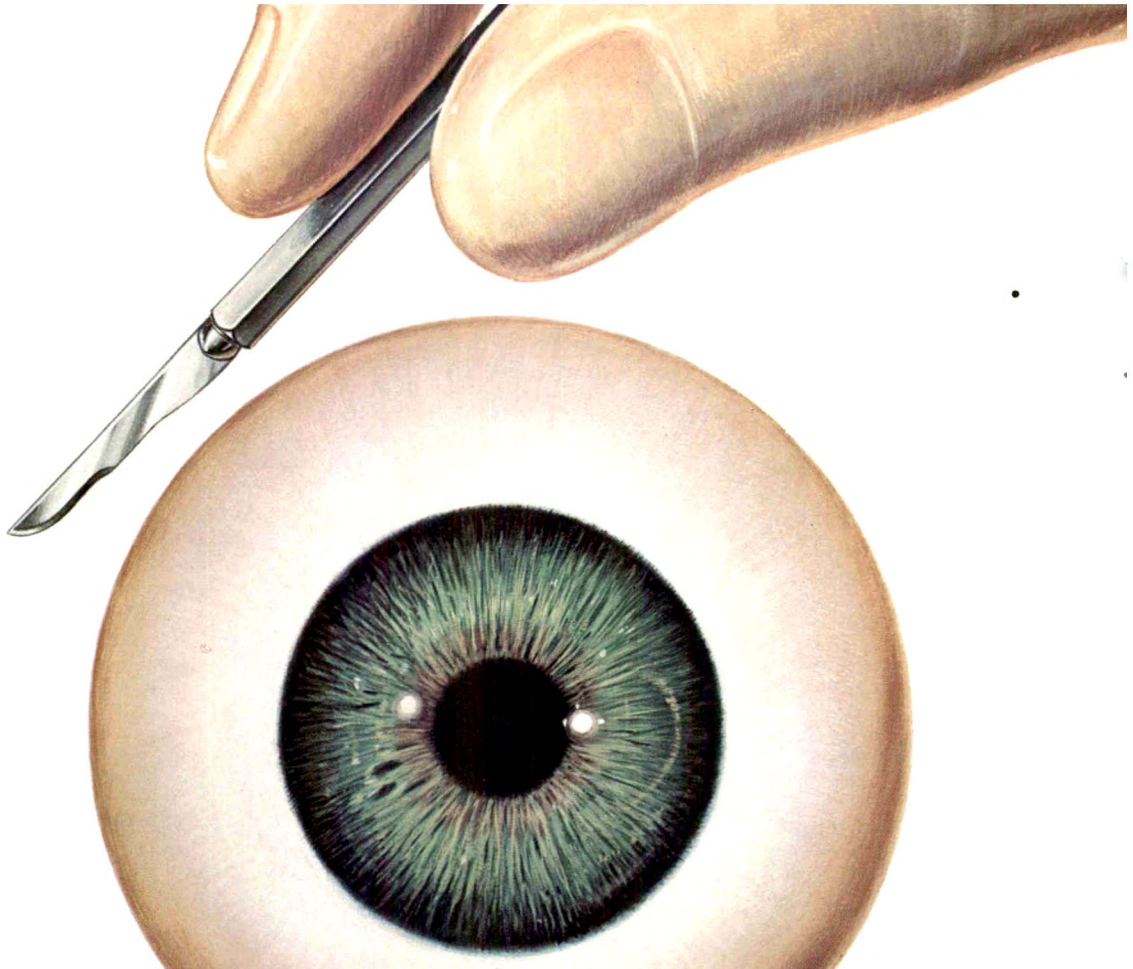
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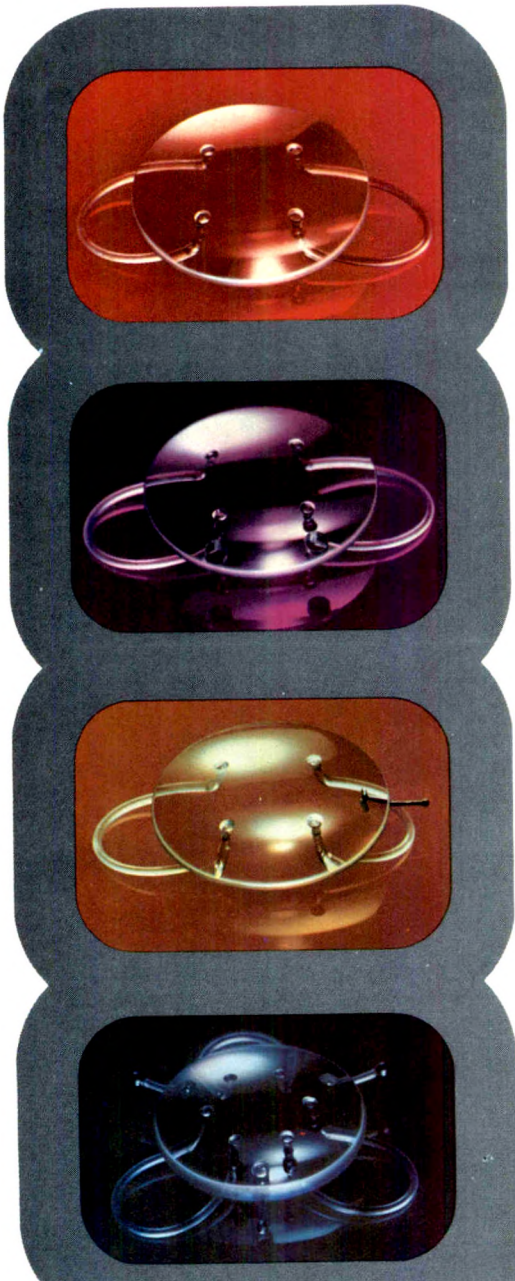
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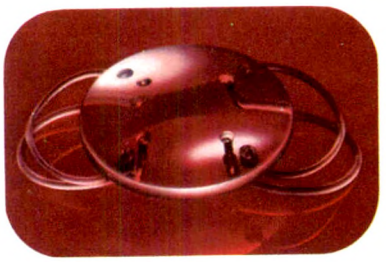
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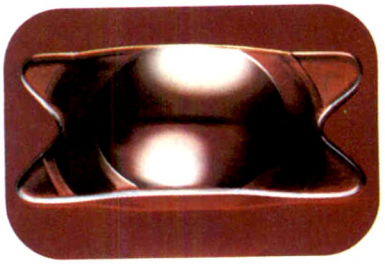
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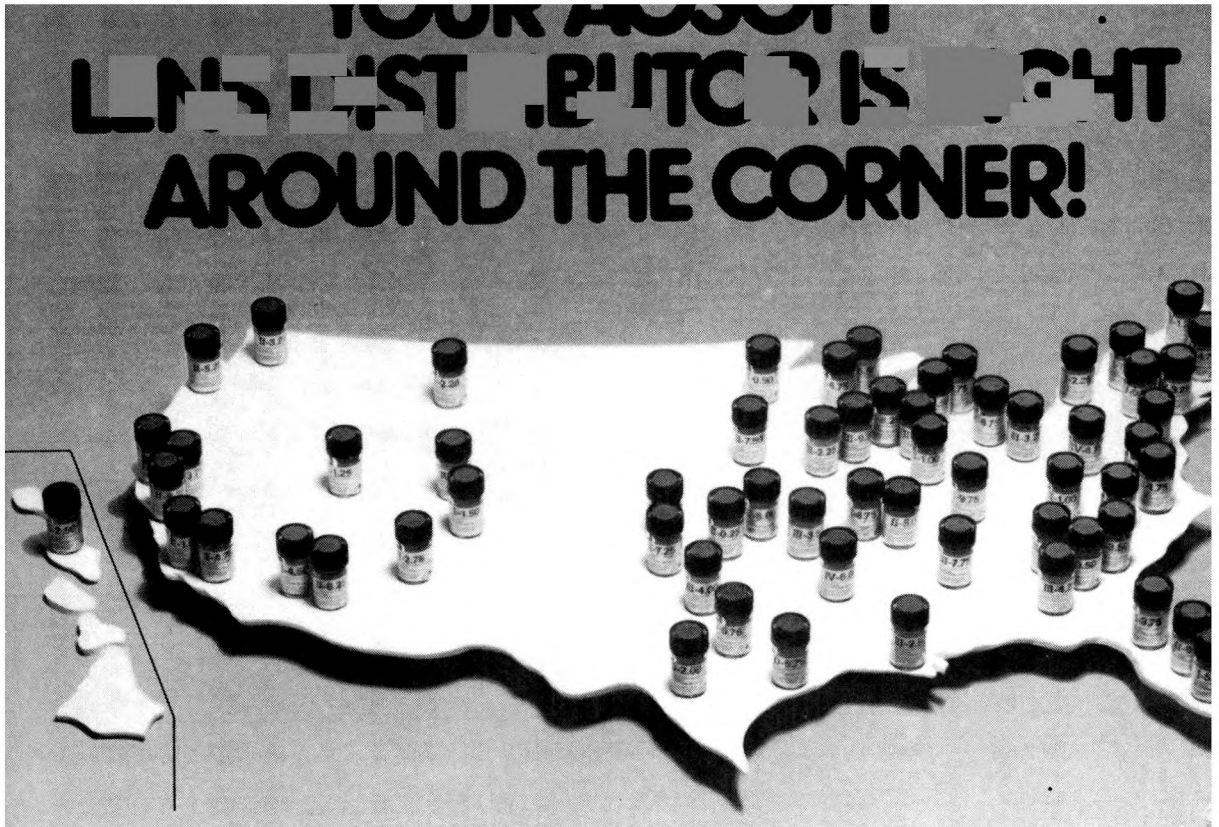
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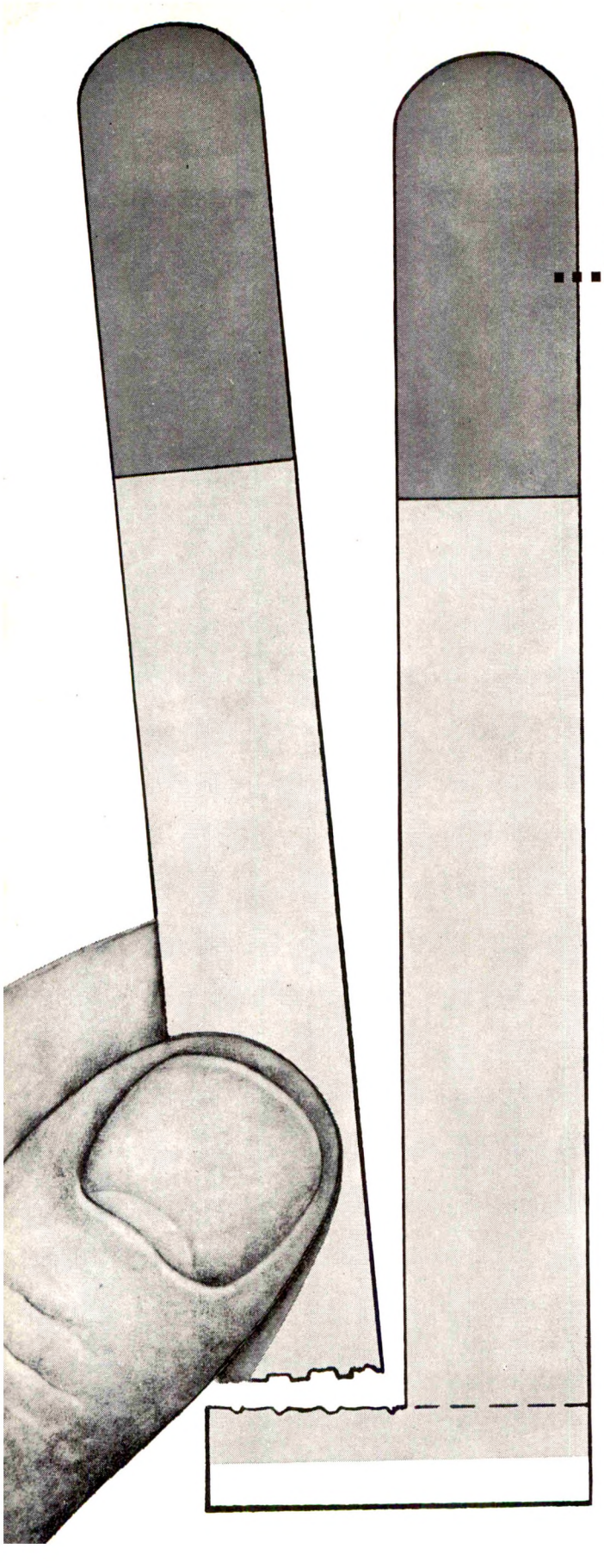
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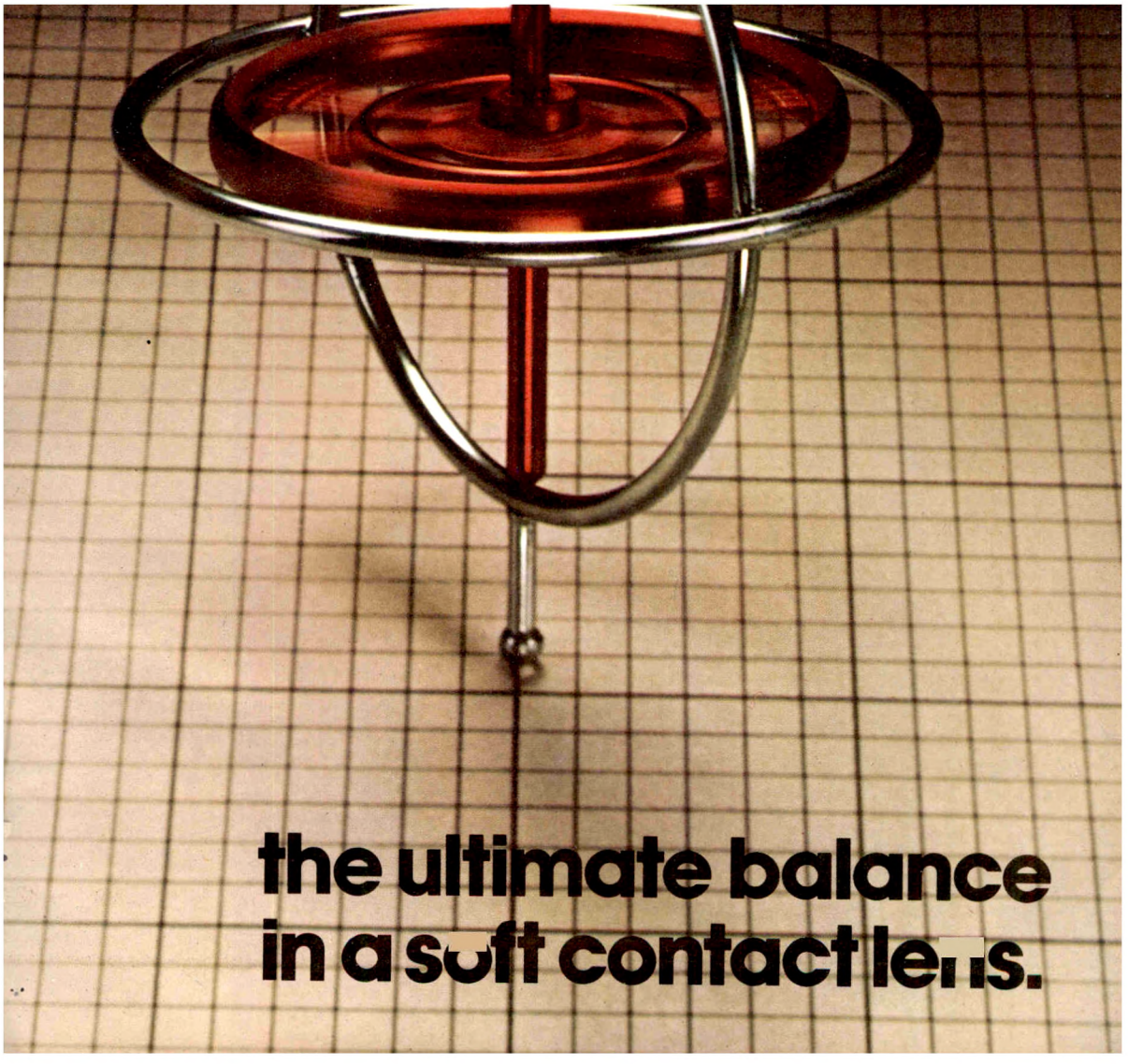
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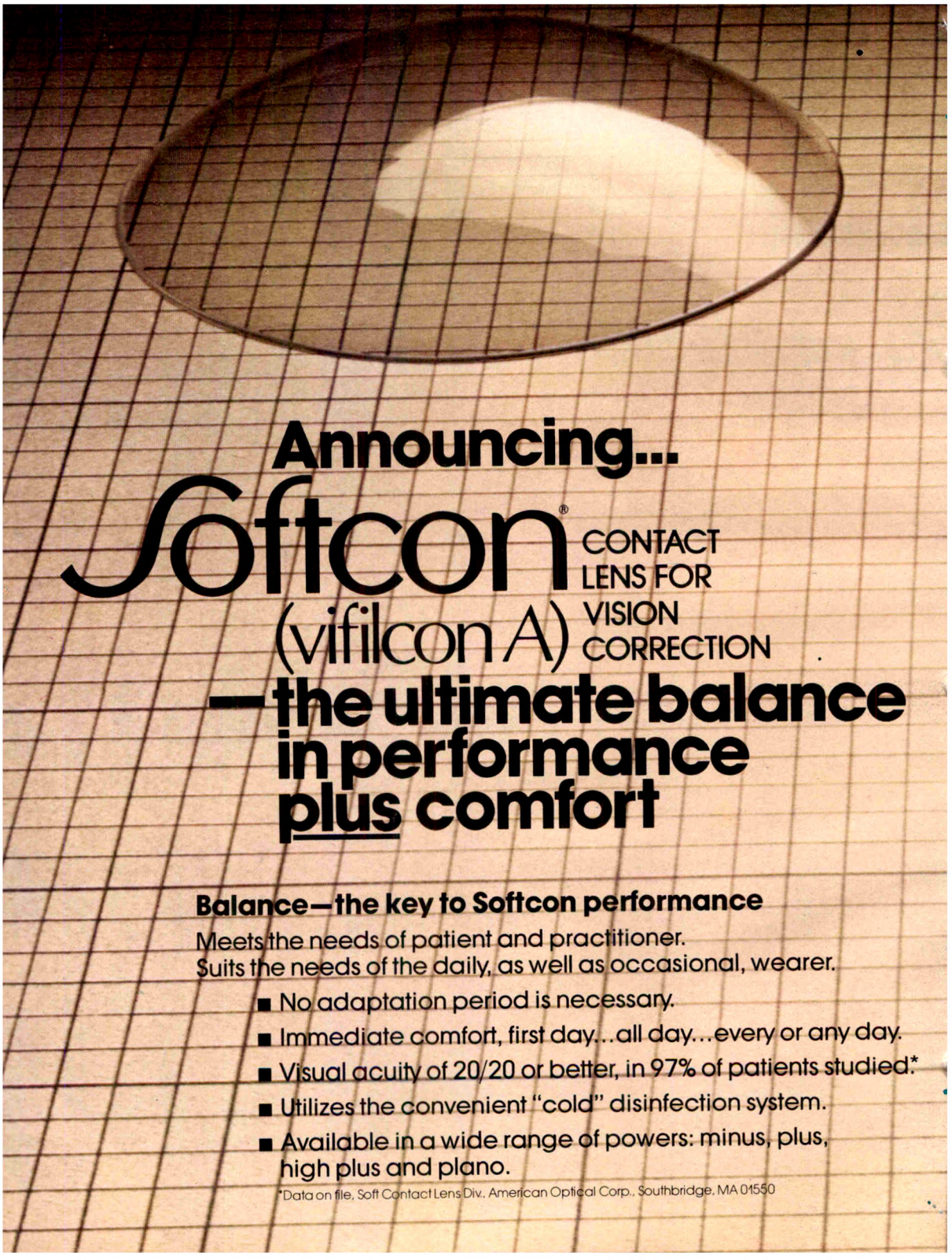
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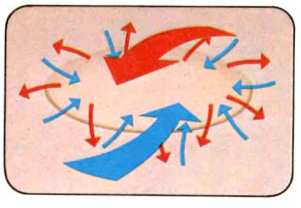

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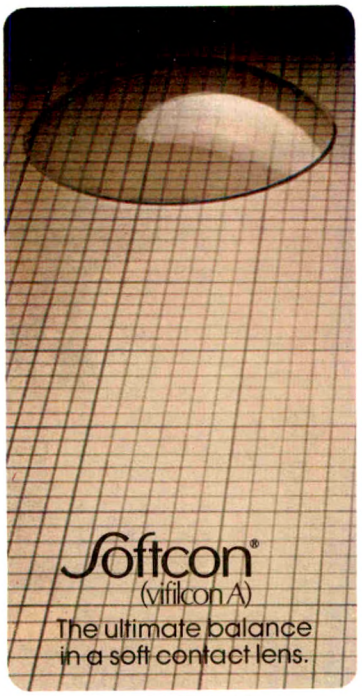
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Vision Correction Use

DESCRIPTION The SOFTCON (vifilcon A) Contact Lens is a hemispherical flexible transparent shell which covers the cornea and part of the sclera. The lens is composed of vifilcon A, a soft hydrophilic plastic co-polymer of 2-hydroxyethyl methacrylate and povidone, USP. The chemical name is: Poly (2-hydroxyethyl methacrylate-co-ethylene dimethacrylate-co-methacrylic acid-g-povidone). When fully hydrated, the lens contains about 55% water by weight.

INDICATIONS The SOFTCON Contact Lens is indicated for the correction of visual acuity in persons with non-diseased eyes and in aphakia. It is indicated for persons who have spherical ametropias, refractive astigmatism usually 1.50 diopters or less and/or corneal astigmatism of 2.00 diopters or less.

CONTRAINDICATIONS Presence of any active infection or inflammation of the eye, insufficient tears, corneal hypoesthesia or any systemic disease which may affect the eye adversely or be exaggerated by wearing contact lenses.

WARNINGS Medications and Eye Drops—The SOFTCON Contact Lens must be stored only in FLEXSOL® soaking solution. **NEVER USE CONVENTIONAL HARD CONTACT LENS PRODUCTS WITH THE SOFTCON CONTACT LENS.** No ophthalmic solutions or medications may be used by SOFTCON Contact Lens wearers immediately prior to or during wear of the lens. No solutions other than PREFLEX®, FLEXSOL, and NORMOL® used for cleaning and chemical disinfection may be used.

Aphakic Patients—Patients who have undergone surgery for cataract removal should not be fitted with SOFTCON Contact Lenses during the immediate post-operative period, until, in the opinion of the surgeon, the eye has healed completely.

Abrasions and Infections—If a lens becomes less comfortable to the wearer than when it was first placed on the cornea, the lens should be removed immediately, and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present, or any abnormal eye condition is observed concurrently with lens wear, the lens should be removed immediately and a clinician must be consulted.

Lens Care—WEARERS MUST ADHERE TO THE RECOMMENDED DAILY CLEANING, CARE AND DISINFECTION REGIMEN AS DESCRIBED IN THE SOFTCON WEARER'S BOOKLET. FAILURE TO ADHERE TO THE RECOMMENDED PROCEDURES MAY RESULT IN THE DEVELOPMENT OF SERIOUS EYE INFECTION.

Wearing Restriction—The lens should be removed before sleeping or swimming, and should not be worn in the presence of irritating fumes or vapors.

Visual Blurring—If unusual visual blurring occurs, the lenses must be removed until the condition subsides. If blurring persists see your eye care practitioner.

PRECAUTIONS Storage—The SOFTCON Contact Lenses must be stored only in FLEXSOL soaking solution. If left exposed to air, the lenses will dehydrate, becoming hard and easily damaged. If a lens dehydrates, it should be carefully handled and soaked again in FLEXSOL until it returns to its normal soft, supple state.

Cleaning and Disinfection—THE SOFTCON CONTACT LENS MUST BE BOTH CLEANED AND DISINFECTED DAILY. ONE PROCEDURE DOES NOT REPLACE THE OTHER.

Cleaning—Daily cleaning is necessary to remove mucus and other deposits which may have accumulated on the lens surface from normal ocular secretions, airborne debris, or handling. The lenses must be cleaned before being disinfected, as deposits on the lens tend to harden and become more difficult to remove after the lenses are disinfected.

Disinfection—Lenses must be disinfected daily according to the chemical disinfection regimen. For chemical disinfection, all three solutions, PREFLEX, FLEXSOL, and NORMOL, must be used and must be changed daily. In the event that the chemical disinfection materials are not available, the lenses should not be worn.

Hygiene—Hands must be washed, rinsed thoroughly and dried with a lint-free towel before handling the lenses. COSMETICS, lotions, soaps, oils and hand creams must not come in contact with the lenses since eye irritation may result. If aerosol sprays are used while the lenses are being worn, the eyes must be kept tightly closed until the sprays have settled.

Fluorescein—Use of fluorescein while the patient is wearing the lenses may cause the lenses to become discolored. Whenever fluorescein is used, irrigate the eyes with preserved normal saline solution, and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein irreversibly.

ADVERSE REACTIONS Serious corneal damage may result from wearing lenses which have been soaked in conventional (hard) contact lens solutions.

Eye irritation may occur within a short time after applying a hypertonic lens. Removal of the lens will relieve the irritation. Very rarely, a lens may adhere to an eye as a result of a patient sleeping with the lens on or while wearing a hypotonic lens. If a lens adheres for any reason, apply a few drops of ADAPETTES® directly to the eye and wait until the lens moves freely before removing it.

Clinical studies indicate that corneal edema as manifested by symptoms such as rainbows or halos around lights, or visual blurring may occur if lenses are worn for too long a time. Removal of the lenses and a rest period of at least one hour generally relieves these symptoms. If symptoms do not subside promptly, or if excess tearing, unusual secretions, or photophobia develop, professional consultation should be obtained.

DOSAGE AND ADMINISTRATION Fitting—Usual methods of fitting conventional (hard) contact lenses do not apply to the SOFTCON Contact Lens.

For a detailed description of the fitting technique, refer to the SOFTCON Fitting Booklet.

Wearing Schedule—The wearing schedule should be determined by the eye care practitioner. Studies have not been performed to support the safety of this lens for longer than the recommended wearing time.

Patients should wear their lenses for 8-16 hours on the day the lenses are dispensed. If patients cannot tolerate 16 hours of lens wear daily, the eyes should be examined and the lens fit re-evaluated.

Lens Care and Handling—Care must be taken on the initial visit to assure that the patient is supplied with a SOFTCON Care Kit and fully understands all proper care and handling procedures for the lenses. As with any contact lens patient, regular re-examination visits are necessary to assure ocular health and patient compliance with instructions.

How Supplied—Each lens is shipped sterile in a sealed glass vial containing buffered normal saline solution. The vial label is marked with the base curve, dioptric power, diameter and the manufacturing identification number of the lens.

Patient Care Kit—The SOFTCON Care Kit is a package required for cleaning, disinfection and storage of the lenses. It consists of the following:

- Carrying & Storage Lens Case
- PREFLEX® Sterile Cleaning Solution
- FLEXSOL® Sterile Disinfection and Storage Solution
- NORMOL® Sterile Rinsing Solution
- ADAPETTES® Sterile Lubricating Solution
- SOFTCON Wearer's Booklet

Caution: Federal law prohibits dispensing without prescription.

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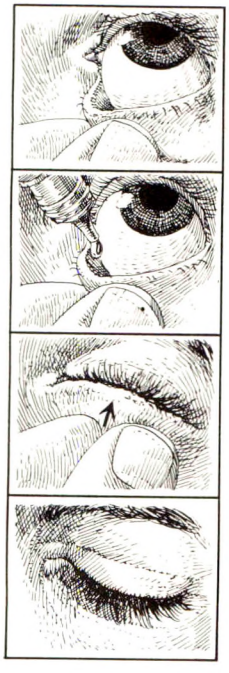
Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 Units; zinc bacitracin 400 Units; neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs.
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Prolonged use may result in overgrowth of nonsusceptible organisms. Ophthalmic Ointment may retard corneal healing.
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2
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3
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1. Fraunfelder FT, Hurwitz J, Marsey M: Presentation at Las Vegas Meeting of Association for Research in Vision and Ophthalmology and the American Academy of Ophthalmology and Otolaryngology, Oct 6, 1976, as reported in *Clinical Trends in Ophthalmology*, April 1977.

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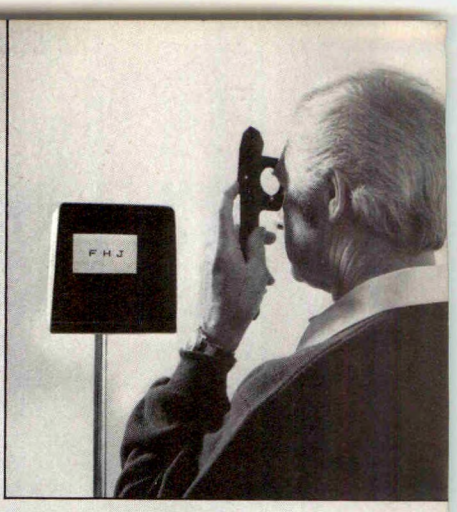
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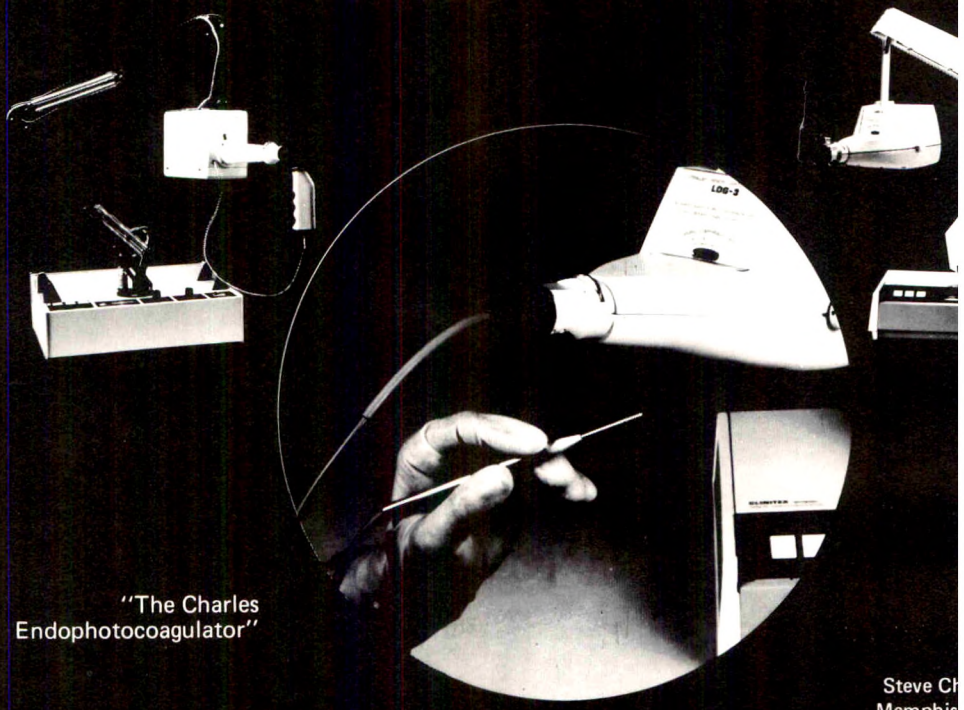
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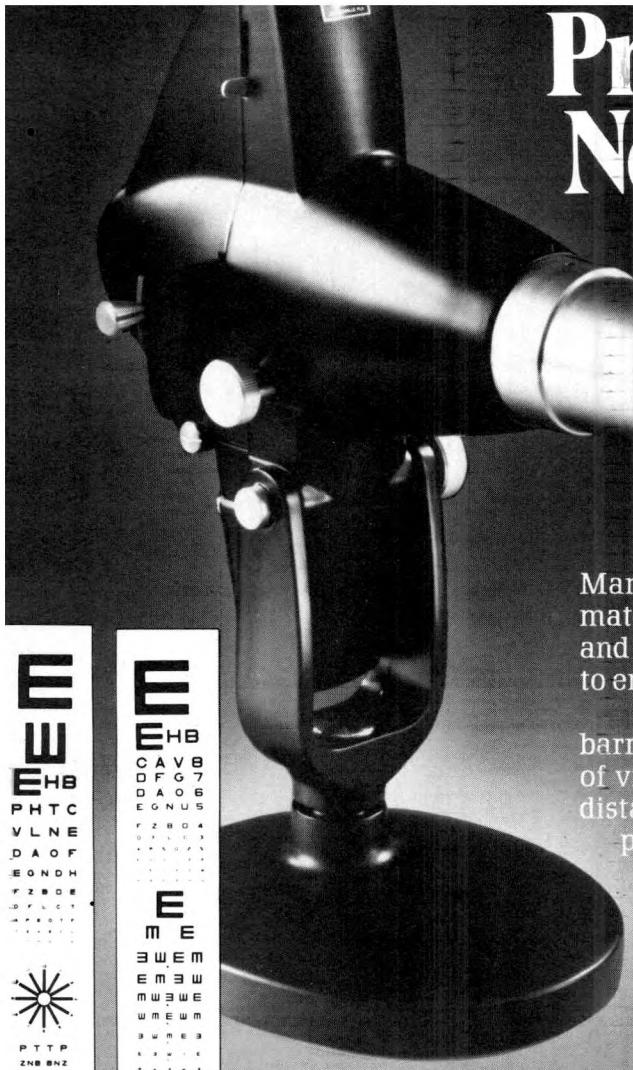
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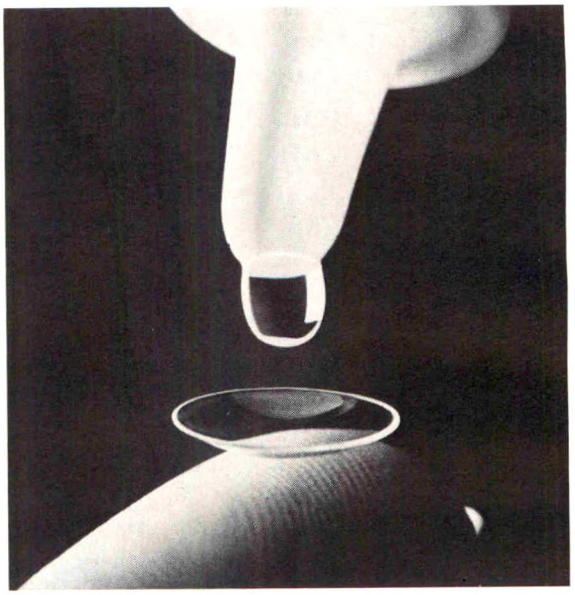
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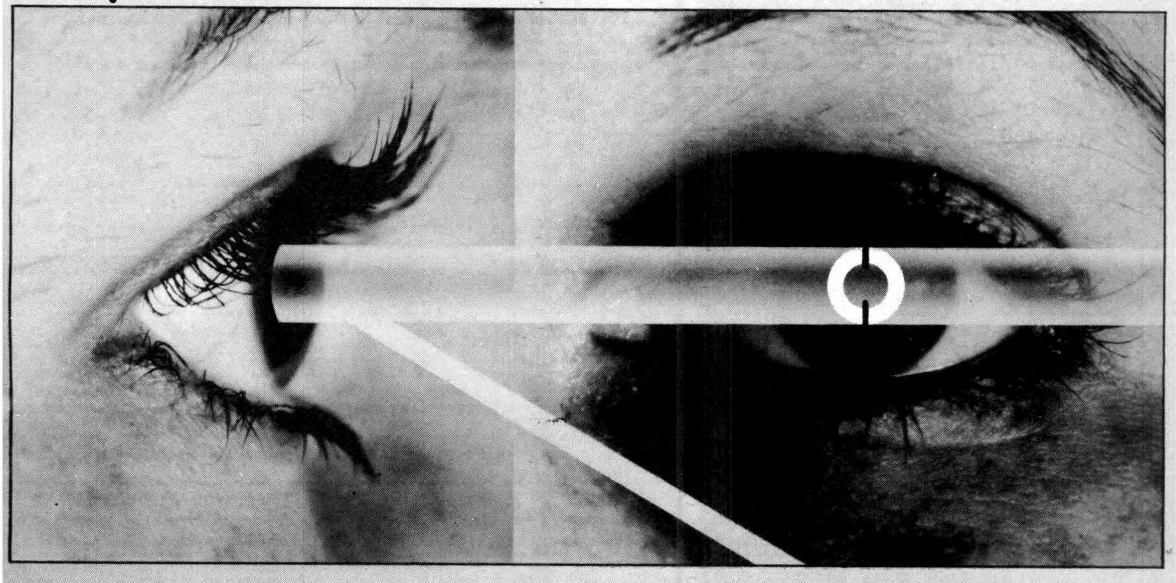
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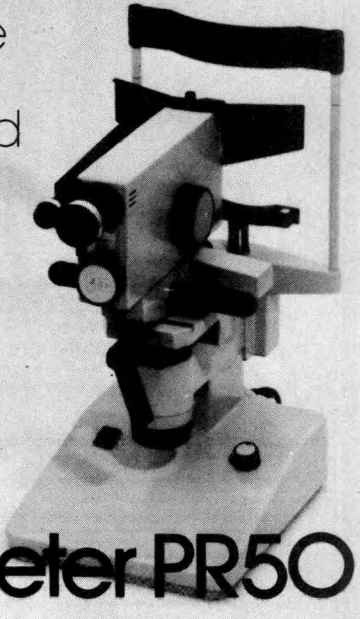
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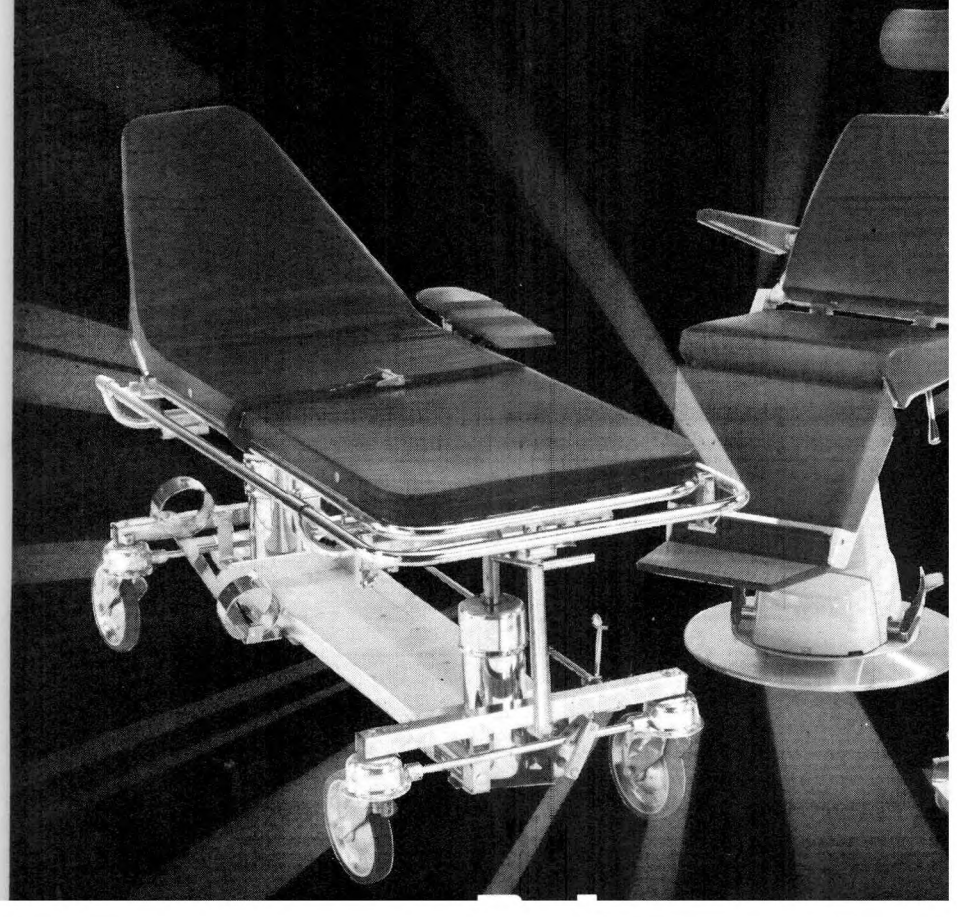
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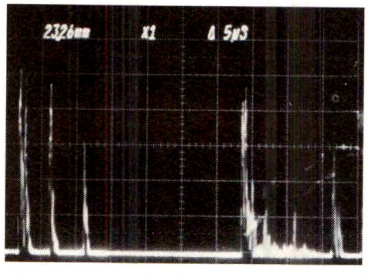
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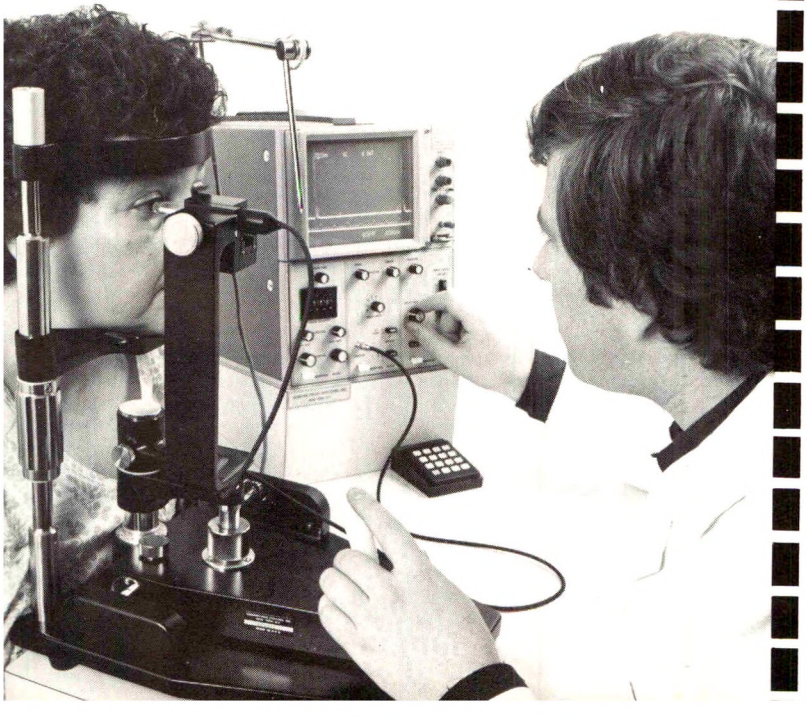
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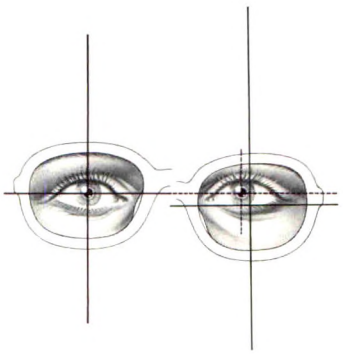
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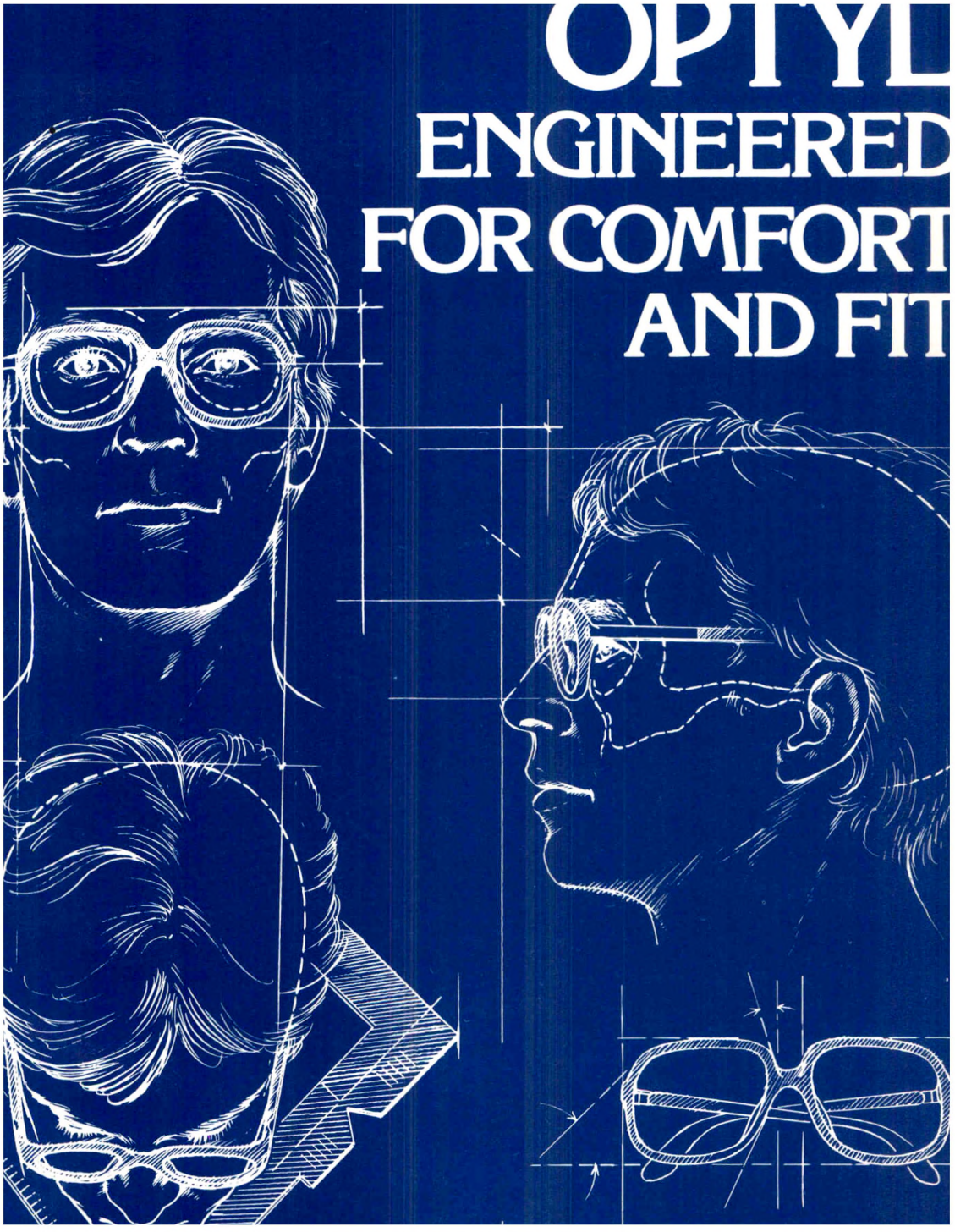


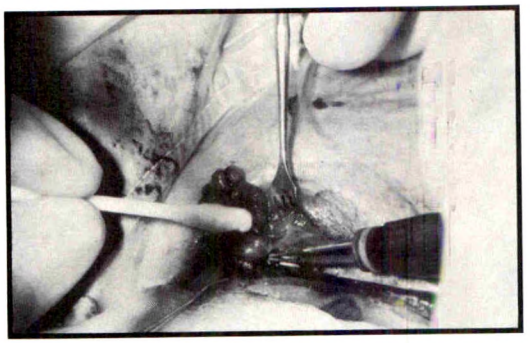
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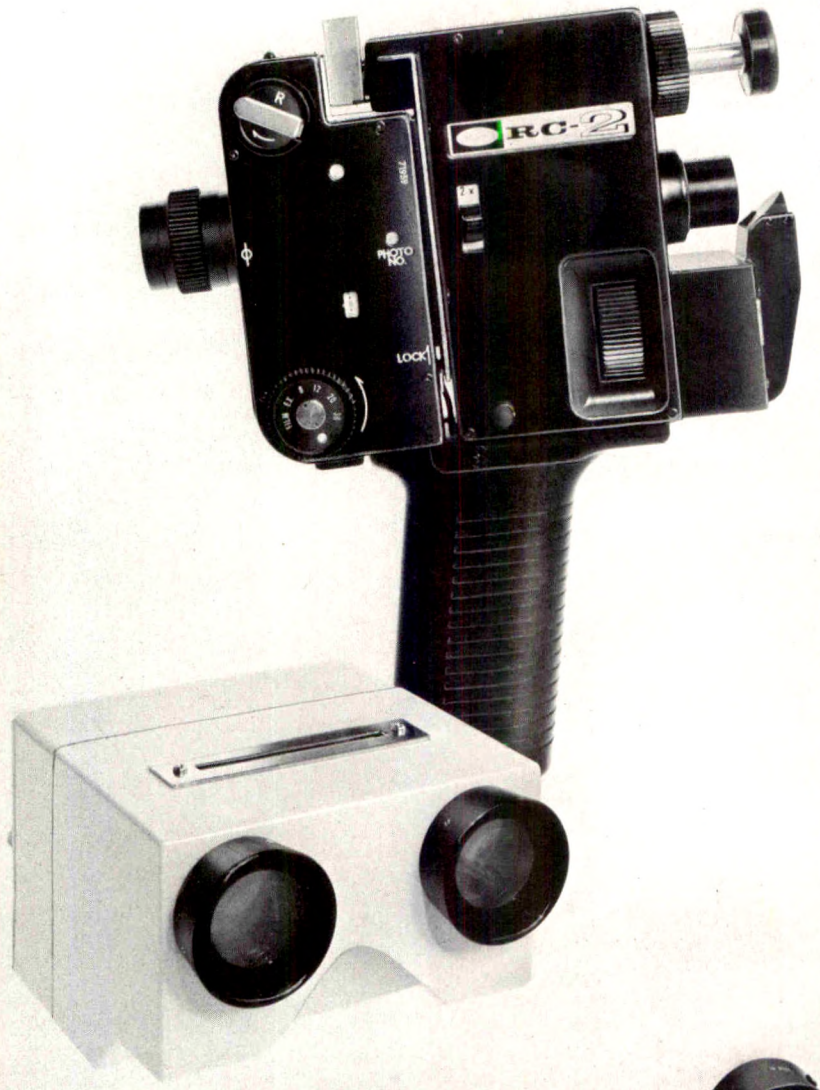
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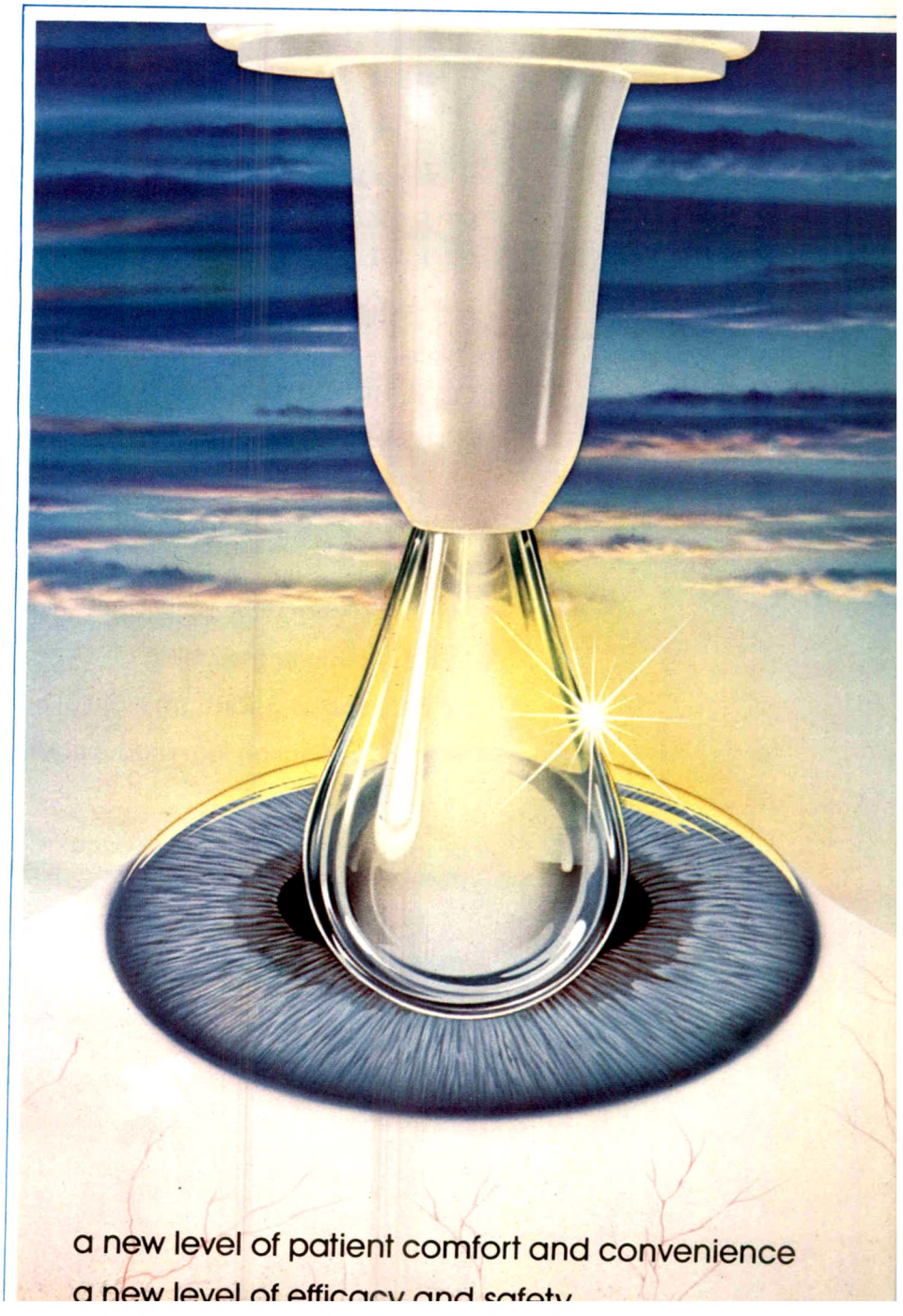
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a significant advance in the topical treatment of chronic open-angle glaucoma...



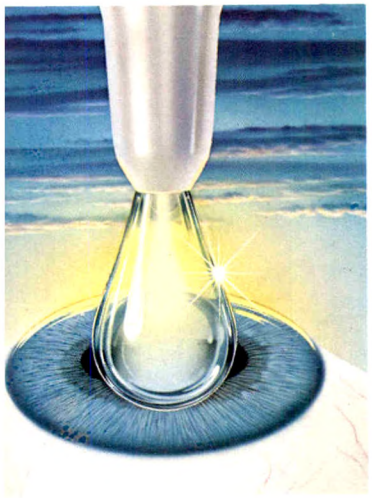
a new level of patient comfort and convenience

a new level of efficacy and safety

MSD

MERCK SHARP & DOHME

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escribing Information,
please see last page
of this advertisement.



new Timoptic™

(TIMOLOL MALEATE | MSD) OPHTHALMIC SOLUTION

a beta-adrenergic blocking agent in ophthalmic solution...for reduction of elevated IOP in chronic open-angle glaucoma

significantly more effective than pilocarpine or epinephrine with fewer and less severe side effects*

- little or no change in pupil size
- little or no blurring of vision
- no dimming of vision...no night blindness
- little or no effect on tear production
- little or no hyperemia
- simple "one-drop" b.i.d. dosage (may encourage long-term compliance)

TIMOPTIC™ (Timolol Maleate, MSD) is contraindicated in patients who are hypersensitive to any component of this product.

Occasionally, mild ocular irritation has been reported.

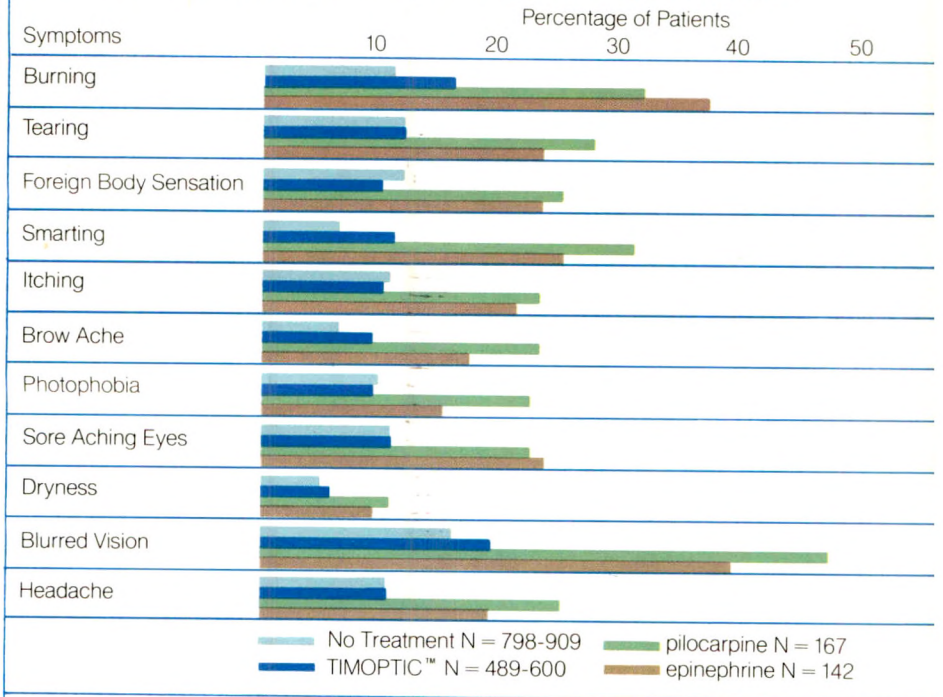
Sufficient clinical data have not been obtained to show safety or efficacy in narrow-angle or angle-closure glaucoma.

*Based on controlled multiclinic studies, evaluating over 1,000 patients. Data on file, Merck Sharp & Dohme. For published articles from the clinical studies on TIMOPTIC,™ please see last page of this advertisement.

a new level of patient comfort and convenience



In clinical studies—a much lower incidence of ocular discomfort than with pilocarpine or epinephrine



Adverse effects commonly caused by pilocarpine and epinephrine as reported in the literature—rarely encountered with TIMOPTIC™ (Timolol Maleate, MSD)

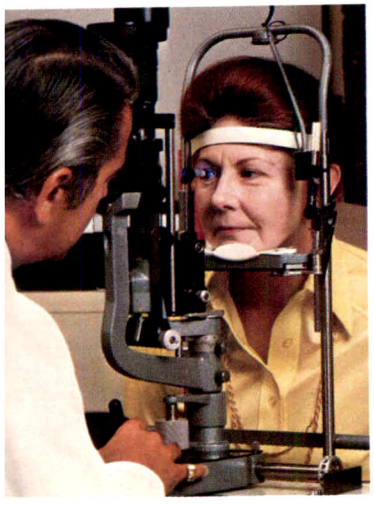
Drug-Induced Adverse Effects

pilocarpine	**TIMOPTIC™ (in clinical studies)**	**epinephrine**	**TIMOPTIC™ (in clinical studies)**
extreme miosis	none reported	conjunctival irritation	rare
spasm of accommodation	none reported	hyperemia	rare and mild
shallowing of the anterior chamber	none reported	macular edema in aphakic patients	none reported
night blindness and dimming of vision	none reported	pigment deposits on lid margins and conjunctiva	none reported
ciliary and conjunctival congestion	rare and mild		

With TIMOPTIC,™ slight reduction of the resting heart rate has been observed in some patients. Local hypersensitivity reactions have occurred rarely.

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new Timoptic™

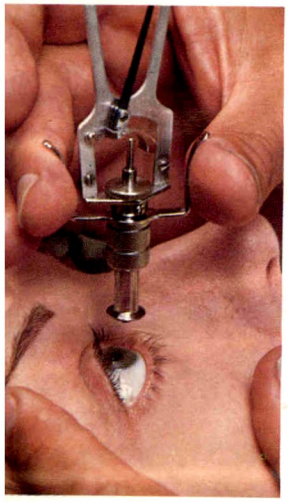
(TIMOLOL MALEATE | MSD) OPHTHALMIC SOLUTION

a beta-adrenergic blocking agent in ophthalmic solution...for reduction of elevated IOP in chronic open-angle glaucoma

- Fast onset of action (usually within ½ hour)
- Based on clinical studies of 638 patients maintained on therapy from 14 to 477 days:
  approximately 76% (485 of 638) of patients satisfactorily managed (IOP less than 22 mm Hg) on TIMOPTIC™ alone
  approximately 93% (593 of 638) of patients satisfactorily managed with TIMOPTIC™ alone or administered concomitantly with other antiglaucoma agents
- No evidence of diminished responsiveness reported in 102 patients treated for at least two years
- Absence of miosis may facilitate visualization of optic disc and evaluation of visual fields
- Usually well tolerated
- Produced fewer and less severe side effects than either pilocarpine or epinephrine

TIMOPTIC™ should be used with caution in patients with known contraindications to systemic use of beta-adrenergic receptor blocking agents. Patients who are already receiving a beta-adrenergic blocking agent orally should be observed for a potential additive effect.

a new level of efficacy and safety



In comparative clinical studies—significantly more effective than pilocarpine or epinephrine

In multiclinic studies, TIMOPTIC™ (Timolol Maleate, MSD) reduced IOP in proportionately more patients





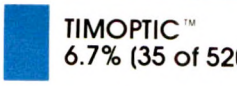




% of patients with IOP reduced to less than 22 mm Hg ($p < 0.01$)

Data are derived from the final visit (week 17) in the multiclinic pilocarpine and epinephrine comparative studies. These include patients who withdrew due to ineffective response or an adverse clinical experience.

In all clinical studies, therapy with TIMOPTIC™ resulted in fewer dropouts* than with pilocarpine or epinephrine





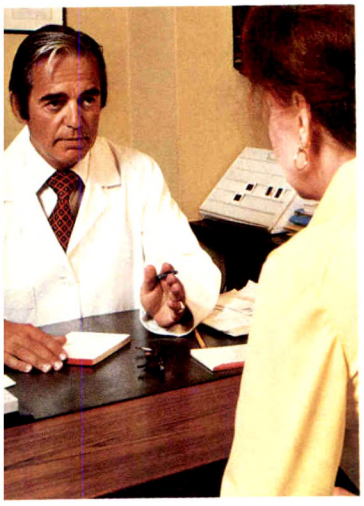


Data include patients participating in clinical studies lasting 14 to 477 days.

*Dropouts are defined as patients whose IOP could not be reduced to levels below 22 mm Hg, or those who withdrew because of an adverse clinical experience.

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new Timoptic™

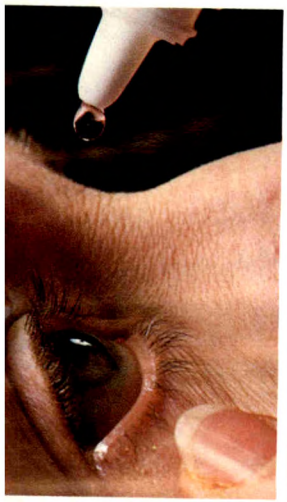
(TIMOLOL MALEATE | MSD) OPHTHALMIC SOLUTION

significantly broadens the medical options in antiglaucoma therapy

- **Permits prolonged maintenance therapy—no evidence of tolerance reported** In a clinical study of 102 patients treated for at least two years, there was no evidence of diminished responsiveness to TIMOPTIC™.
- **Compatible with other agents** Concomitant therapy with pilocarpine and other miotics, and/or epinephrine, and/or systemically administered carbonic anhydrase inhibitors, such as acetazolamide, can be instituted for the patient who needs reduction of IOP greater than provided by one drop of 0.5% TIMOPTIC™ twice a day. Dosages above one drop of 0.5% TIMOPTIC™ twice a day generally have not been shown to produce further reduction in intraocular pressure.
- **Helpful in the medical management of a broader range of patients** In some patients who respond inadequately to maximum available drug therapy, the addition of TIMOPTIC™ may result in satisfactory management of intraocular pressure, thus possibly postponing the need for surgery.
- **Often effective in patients previously difficult to manage**...such as working patients incapacitated by accommodative spasm produced by miotics, older patients with cataracts whose vision is impaired with miotics, patients with heavily pigmented irides whose response to pilocarpine is diminished, and aphakic patients who may develop macular edema from epinephrine.

Since clinical studies in children have not been done, TIMOPTIC™ is not recommended for use in children at this time. TIMOPTIC™ has not been studied in human pregnancy. The use of TIMOPTIC™ in pregnant women requires that the anticipated benefits be weighed against the possible hazards.

a beta-adrenergic blocking agent in ophthalmic solution...for reduction of elevated IOP in chronic open-angle glaucoma



Dosage Guidelines:

How to transfer from current therapy to TIMOPTIC™ (Timolol Maleate, MSD):

1 On the first day: continue with the agent(s) already being used and add one drop 0.25% TIMOPTIC™ in each eye b.i.d.

2 On the second day: discontinue the previously used agent(s) and continue with TIMOPTIC™ in each eye b.i.d.

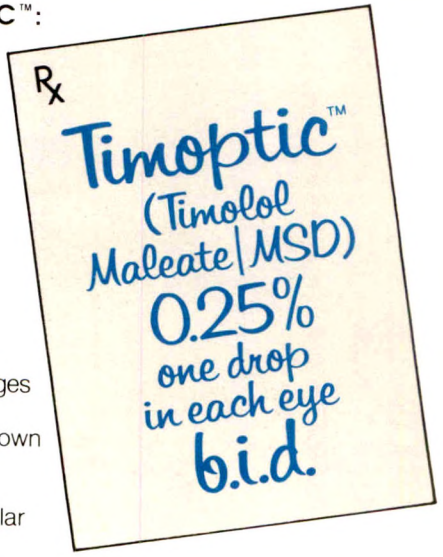
How to add TIMOPTIC™ to other agents:

1 Administer one drop 0.25% TIMOPTIC™ in each eye b.i.d....while continuing with the agent(s) already being used.

2 If a higher dosage of TIMOPTIC™ is required, substitute one drop 0.5% TIMOPTIC™ in each eye b.i.d....while continuing with the agent(s) already being used.

How to start patients on TIMOPTIC™:

Usual starting dosage:
one drop 0.25% TIMOPTIC™
in each eye twice a day.



If clinical response is not adequate:

Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC™ twice a day in each eye. If the intraocular pressure is maintained at satisfactory levels, the dosage schedules may be changed to one drop once a day in each eye. Dosages above one drop of 0.5% TIMOPTIC™ twice a day generally have not been shown to produce further reduction in IOP.

Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

In patients with a history of severe cardiac disease, pulse rates should be checked.

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For a brief summary of Prescribing Information, please see following page.

for many patients—a significant advance for the reduction of elevated IOP

- in chronic open-angle glaucoma
- in ocular hypertension
- in aphakic glaucoma
- in some patients with secondary glaucoma

new Timoptic™

(TIMOLOL MALEATE | MSD) OPHTHALMIC SOLUTION



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10. Zimmerman, T. and Kaufman, H.: Timolol: a new drug for the treatment of glaucoma?, in *Symposium on Ocular Therapy*, ed. I. H. Leopold, vol. 10, New York, John Wiley & Sons, 1977, pp. 69-76.
11. Zimmerman, T. and Kaufman, H.: Timolol: Dose response and duration of action, Arch. Ophthalmol. *95(4)*:605-607, April 1977.

CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients who are hypersensitive to any component of this product.

PRECAUTIONS: Should be used with caution in patients with known contraindications to systemic use of beta-adrenergic receptor blocking agents. These include bronchial asthma; sinus bradycardia and greater than first-degree block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure; concomitant use with adrenergic-augmenting psychotropic drugs. In patients with a history of severe cardiac disease, pulse rates should be checked. Patients who are already receiving a beta-adrenergic blocking agent orally and who are given TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blocka

Sufficient clinical data have not been obtained to show safety or efficacy in narrow-angle or angle-closure glaucoma.

Pregnancy: TIMOPTIC has not been studied in human pregnancy. The use of TIMOPTIC in pregnant women requires that the anticipated benefit be weighed against possible hazards.

Use in Children: Since clinical studies in children have not been done, TIMOPTIC is not recommended for use in children at this time.

ADVERSE REACTIONS: Occasionally, signs and symptoms of mild ocular irritation have been reported. Slight reduction of the resting heart rate (mean reduction 2.9 beats/minute, standard deviation 10.2) has been observed in some patients. Local hypersensitivity reactions have occurred rarely.

Note: TIMOPTIC has been used in patients with glaucoma wearing conventional (PMMA) hard contact lenses, and has generally been well tolerated. TIMOPTIC has not been studied in patients wearing lenses made with materials other than PMMA.

HOW SUPPLIED:

TIMOPTIC Ophthalmic Solution, 0.25%
TIMOPTIC Ophthalmic Solution, 0.5%
Both are available in 5-ml plastic OCUMETER® Ophthalmic Dispenser with a controlled drop tip

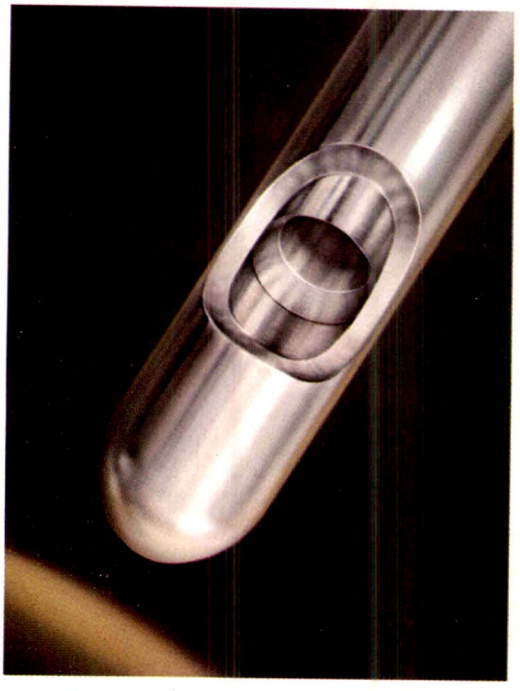
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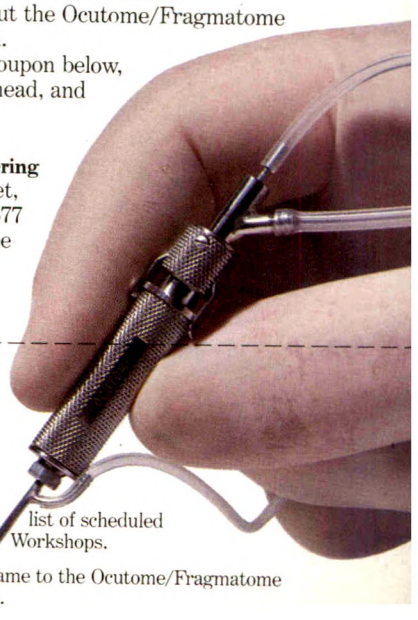
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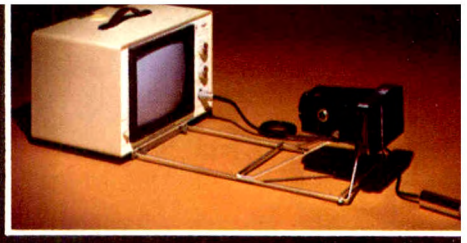
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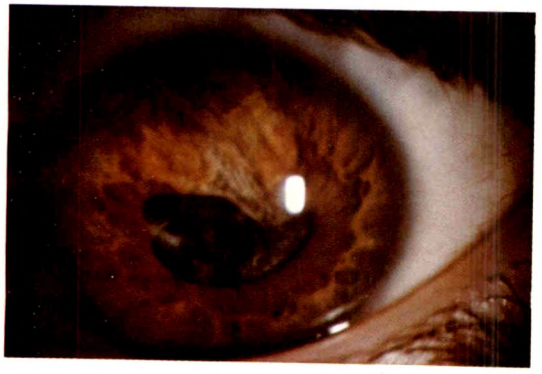
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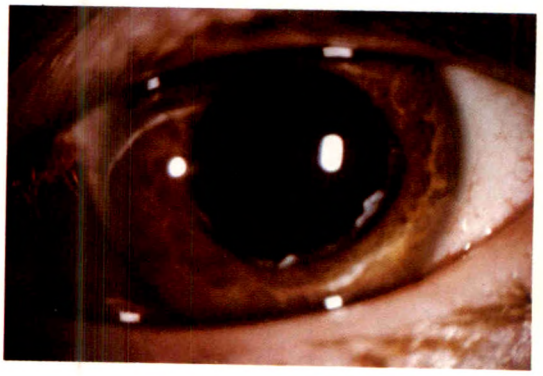
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Eye before operation



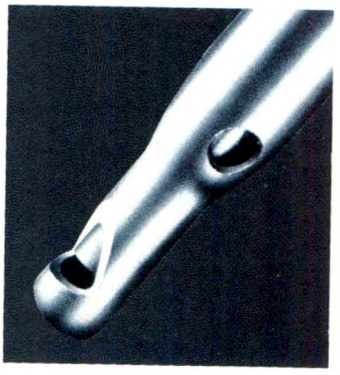
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Extracapsular Cataract Extraction with Intraocular Lens Course
Richard Kratz, M.D., Director
Lawrence Hyde, M.D.
David McIntyre, M.D.
Unlimited attendance Free

Suturing Techniques and Safeguards Course
William Simcoe, M.D., Director
Unlimited attendance Free

Use of McReynolds Instruments Course
William McReynolds, M.D., Director
Unlimited attendance Free

Kelman Anterior Chamber Lens Course
Charles Kelman, M.D., Director
Unlimited attendance Free

Tuesday, April 10

Lens Calculation Course
Kenneth J. Hoffer, M.D., Director
Charles Cleavenger, M.D.
H. John Shammas, M.D.
Limited attendance 100 $50

Intracapsular Cataract Extraction with Intraocular Lens Course
Robert C. Drews, M.D., Director
Unlimited attendance Free

Extracapular Cataract Extraction with Intraocular Lens Course
Henry Hirschman, M.D., Director
Unlimited attendance Free

Malpractice Course
Herve Byron, M.D., Director
Unlimited attendance Free

McCannel Suture Course
Malcolm McCannel, M.D., Director
Unlimited attendance Free

Anterior Chamber Lens Course
Jerald Tennant, M.D., Director
Unlimited attendance Free

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DT PD _____ AMT PD _____ PK MD _____ CD NO _____

REGISTRATION • U.S. INTRAOCULAR LENS SYMPOSIUM

COST

Prior to Mar. 1: ☐ Members, Fellows and Military of AIOIS $325
☐ Non-Members $400 ☐ Residents $175 ☐ Nurses and Technicians $125
☐ Lens Calculation Course $50 ☐ Endothelial Photography Course $100

After Mar. 1: ☐ Members, Fellows and Military of AIOIS $375
☐ Non-Members $450 ☐ Residents $225 ☐ Nurses and Technicians $150
☐ Lens Calculation Course $50 ☐ Endothelial Photography Course $100

☐ Check here if you wish further information on the Ladies' Program

EACH REGISTRANT MUST FILL OUT A SEPARATE FORM. Cancellations: 90% refund prior to postmark date of March 1. 10% refund after postmark date of March 1. Residents must have letter from Chief of department. Make check or money order payable to: U.S. Intraocular Lens Symposium and send with this form to P.O. Box 3140, Santa Monica, California 90403. For hotel reservations, please contact Century Plaza Hotel directly at: Avenue of the Stars, Los Angeles, California 90067. Telephone (213) 277-2000. Toll free reservation number: 1 (800) 228-3000 When making reservations please indicate that you are with the AIOIS.

Name _____

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City _____ State _____

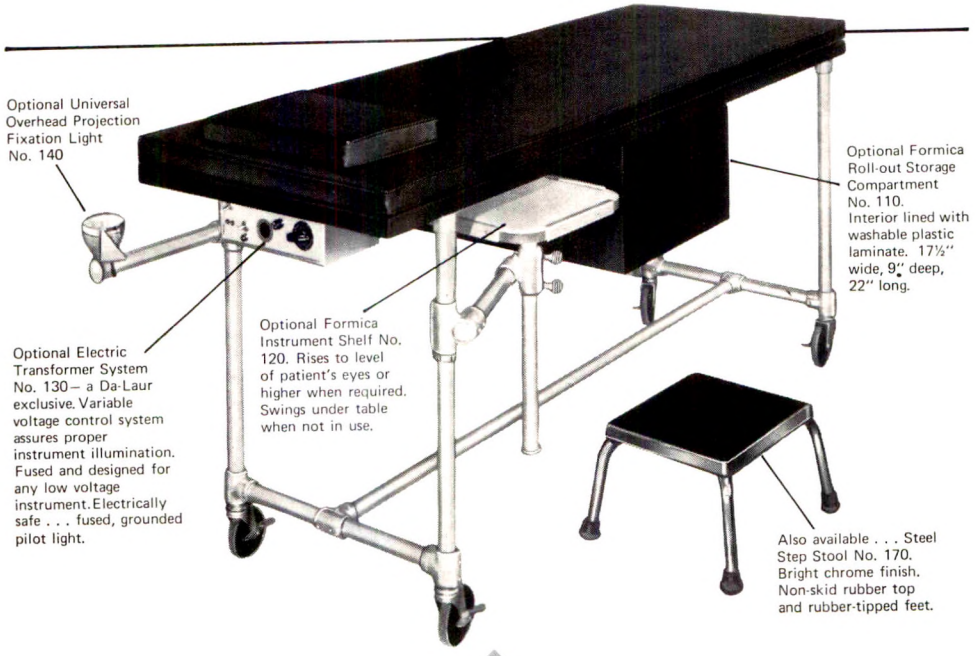
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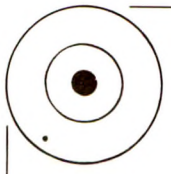
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MID-WINTER NATIONAL MEETING

CONTACT LENS ASSOCIATION OF OPHTHALMOLOGISTS

January 12-14, 1979 • Sahara Hotel, Las Vegas, Nevada

16 Hours CME Credits—AMA Category I

ELEVENTH CONRAD BERENS LECTURE
Jorge N. Buxton, M.D.
Post Surgical Visual Rehabilitation

DISTINGUISHED VISITING LECTURER
Jose I. Barraquer, M.D.
Present Status of Keratophakia for the Correction of Hyperopia and Aphakia

THIRD ANNUAL THEODORE E. OBRIG MEMORIAL LECTURE
Mr. Jack Moore
A Practical Approach for the Average Clinical Practice

PRACTICE MANAGEMENT SEMINAR

Herschell H. Boyd, M.D., Chairman

Immediately preceding its Mid-Winter National Meeting, CLAO offers this optional Practice Management Seminar on Thursday, January 11, 1979, from 9:00 a.m. to 5:00 p.m. There is no additional registration fee for this Seminar.

OPENING REMARKS

Oliver H. Dabezies, Jr., M.D., F.A.C.S.
Chairman, Mid-Winter Meeting

Jack Hartstein, M.D.
Outgoing President

Herbert E. Kaufman, M.D., F.A.C.S.
CLAO President

H. H. Boyd, M.D.
Chairman, Practice Management Seminar

Symposium: OPHTHALMOLOGISTS' USE OF COMPUTERS
Paul R. Honan, M.D., Moderator

Computer in the Office ..... Philip C. Hessburg, M.D.
Computer Assisted Contacts ..... Arthur S. Rathkey, M.D.
Computer Billing Service ..... Herve M. Byron, M.D.
Pitfalls in Computer Billing ..... Herschell H. Boyd, M.D.

Questions from Audience

Symposium: OFFICE MANAGEMENT
J. Elliott Blaydes, M.D., Moderator

Efficient Use of a Large Staff ..... J. Elliott Blaydes, M.D.
My Most Useful Aid ..... Herve M. Byron, M.D.
How I Refract ..... Thomas R. Mazzocco, M.D.
Why I Hired a Business Manager ..... J. Elliott Blaydes, M.D.
My Most Useful Aid ..... Paul R. Honan, M.D.
Automated Refractor ..... Melvin I. Freeman, M.D.

Questions from Audience

Symposium: DISPENSING CONTACT LENSES
Harold A. Stein, M.D., Moderator

My Best System ..... Robert H. Hales, M.D.
Efficient Aids ..... Harold A. Stein, M.D.
Practice Limited to Contacts ..... Joseph A. Baldone, M.D.
Office Techniques ..... Jack Hartstein, M.D.
Hard or Soft ..... Herschell H. Boyd, M.D.
Film "Con-tac-ties" ..... J. Elliott Blaydes, M.D.
Questions from Audience

Symposium: SURVIVAL IN THE 1980's
Herschell H. Boyd, M.D., Moderator

Should I Incorporate ..... Richard P. Kratz, M.D.
Professional Advice ..... Greg G. Schoff, M.D.
Apartment House Ventures ..... J. Harley Quint, M.D.
Education Materials ..... Dean M. Rockey, M.D.
Dispensing of Glasses ..... R. Hugh Minor, M.D.
Business of Farming ..... Francis C. Hertzog, Jr., M.D.
Conservative Areas ..... Herschell H. Boyd, M.D.
Questions from Audience

MID-WINTER NATIONAL MEETING

Friday, January 12

CONTACT LENS PRESENTATIONS
Jack Hartstein, M.D., Presiding

Symposium: INDUSTRIAL SAFETY AND CONTACT LENSES
J. Elliott Blaydes, M.D., Moderator
Joseph F. Novak, M.D., Arthur H. Keeney, M.D., Robert J. Crossen, M.D., and Carole West, M.D.
Consultants to Committee: G. Peter Halberg, M.D.,F.A.C.S., Jorge N. Buxton, M.D.

Symposium: PROLONGED WEAR - UPDATE
Walter J. Stark, M.D., Moderator
Jorge Buxton, M.D., Richard H. Keates, M.D., and Anthony J. Nesburn, M.D.

Mary Bruch
Food and Drug Administration

THIRD ANNUAL THEODORE E. OBRIG MEMORIAL LECTURE
Mr. Jack Moore
A Practical Approach for the Average Clinical Practice

SPORTS AND CONTACT LENSES
Richard H. Keates, M.D.

DISTINGUISHED VISITING LECTURER
Jose I. Barraquer, M.D.
Present Status of Keratophakia for the Correction of Hyperopia and Aphakia

CONTACT LENS COURSES-Section I

(Pre-registrants may select courses by mail)

The Extended Wear of Soft Contact Lenses
Director—Perry S. Binder, M.D.
Instructors—Richard Keates, M.D. and Edward Shaw, M.D.

Management of Corneal and Contact Lens Problems
Director—Robert A. D'Amico, M.D.
Instructors—Joseph A. Baldone, M.D. and John F. Morgan, M.D.

How to Select the Best Soft Lens for Your Patient
Director—Ellis Gruber, M.D.

Management of the Contact Lens Problem Case
Director—G. Peter Halberg, M.D.

Soft and Hard Contact Lens Fitting with Custom Design Lenses
Director—Herschell H. Boyd, M.D.
Instructor—Paul R. Honan, M.D.

Fitting of Oxygen Permeable Contact Lenses
Director—Jay Lippman, M.D.

Review of Hard & Soft Lens Technology
Director—Joseph W. Soper
Instructors—Kenneth W. Swanson, Frank B. Sanning, Ralph T. Sutton, and Jack W. Moore

Therapeutics & Cosmetic Scleral Contact Lenses
Director—Herbert L. Gould, M.D.
Instructors—John W. Espy, M.D. and Leroy G. Meshel, M.D.

Contact Lens Fitting in Infants and Children
Director—Harold P. Koller, M.D.
Instructors—Anthony Caputo, M.D., Jerry Maida, M.D., and J. Matthew Robinoweiz, M.D.

Modification of Hard Contact Lenses
Director—Marvin A. Garland, M.D.
Instructors—Paul Honan, M.D. and Vic Brown

CONTACT LENS COURSES-Section II

(Pre-registrants may select courses by mail)

Hydrogel Lathe Lenses Versus Cast Lenses
Director—Chester J. Black, M.D.

Utilization and Training of a Contact Lens Technician
Director—Robert J. Crossen, M.D.

Therapeutic Uses of Soft Contact Lenses
Director—Edward Shaw, M.D.
Instructors—Frederick Brightbill, M.D., Walter Stark, M.D., and Robert G. Webster, M.D.

The Aquaflex Hydrophilic Lens - Review of Vault Theory of Fitting, Research and Clinical Experience
Director—Ellis Gruber, M.D.
Instructors: Harold A. Stein, M.D., Stanley Gordon, Ph.D., Paul Bingham

Keratoconus
Director—Frank B. Hoefle, M.D.
Instructors—Richard G. Lembach, M.D., Jorge N. Buston, M.D., James Koverman, and Delmar R. Caldwell, M.D.

Specialized Techniques of Lens Fitting
Director—Joseph W. Soper
Instructors—James C. Tannehill, Vernon R. Lamb, and William McGuire

Bifocal and Multifocal Contact Lenses for the Presbyope & Aphake
Directors—Abraham Schlossman, M.D., and Frank J. Weinstock, M.D.
Instructors—Carolyn Schlossman, Norman Schmid, Sr., and Ronald Akashi, M.D.

Clinical Aspects of Fitting the Hydrocurve Lens
Director—James S. Russell, M.D.
Instructor—Gerald Feldman, Ph.D.

Extended Contact Lens Wear
Director—Anthony B. Nesburn, M.D.
Instructors—Dwight H. Cavanagh, M.D., Steven Kelly, M.D., and Roger Langston, M.D.

Astigmatism Correction with Hard & Soft Contact Lenses
Director—Paul Honan, M.D.
Instructors—Whitney Sampson, M.D.

Saturday, January 13

INTRAOCULAR LENS PRESENTATIONS

Jorge N. Buxton, M.D., Presiding

Symposium: THE CONTACT LENS CORRECTION OF ASTIGMATISM

Joseph A. Baldone, M.D., Moderator

Correction of High Corneal Cylinders by the Use of Piggy-back Technique ..... Joseph A. Baldone, M.D.
Fitting of Soft Front-surface Toric Lenses Produced by Wesley-Jessen ..... Barry A, Maltzman, M.D.
Other Participants: Whitney G. Sampson, M.D., Harold A. Stein, M.D., Mr. James Tannehill, Dr. Philippe Baronet

---

Symposium: ASTIGMATISM - SURGICAL CORRECTION

Herbert E. Kaufman, M.D., Moderator

The Practical Application of Keratomileusis and Keratophakia ..... Miles Friedlander, M.D.
New Approaches to the Management of Refractive Errors ..... Randall Olson, M.D.
The Troutman Relaxing Incision, A New Technique for Management of Astigmatism ..... Richard C. Troutman, M.D.

THE FUTURE WAS YESTERDAY

Lawrence A. Winograd, M.D.

ELEVENTH CONRAD BERENS LECTURE
Jorge N. Buxton, M.D.
Post Surgical Visual Rehabilitation

Symposium: PITFALLS IN LENS IMPLANTATION
Harold A. Stein, M.D., Moderator

Errors in Patient Selection ..... Harold A. Stein, M.D.
Pitfalls at the Time of Surgery ..... Richard Kratz, M.D.
Pitfalls in the Immediate Post-op Period ..... Marvin Kwitko, M.D.
Pitfalls in the Late Post-op Period ..... Herve Byron, M.D.
Guiding the Resident in Lens Implantation ..... Leeds Katzin, M.D.
Question and Answer Period

Symposium: SURGICAL KERATOMETRY
Herbert E. Kaufman, M.D., Moderator
Participants: Cliff Terry, M.D., Richard C. Troutman, M.D.

Qualitative Microsurgical Keratometry, An Essential to the Understanding of Corneal Dynamics ..... Richard C. Troutman, M.D.

Symposium: SURGICAL TECHNIQUES FOR VARIOUS IMPLANTS (Movies)
Jack Hartstein, M.D., Moderator

Technique with the Copeland Lens ..... Ned Snyder, M.D.
Technique with the Copeland Lens ..... William U. McReynolds, M.D.
Medallion Lens in Association with Intracapsular Cataract Extraction ... Manus C. Kraff, M.D.
2-Loop Binkhorst Lens ..... Richard Kratz, M.D.
4-Loop Binkhorst Lens ..... Henry Hirschman, M.D.
Federov Sputnik Lens and the Platinum Clip Lens ..... Marvin L. Kwitko, M.D.
Primary Implants of the Choyce Lens ..... Jerald L. Tennant, M.D.
Secondary Implantation of the Azar Tripod ..... Robert Azar, M.M.D.
Shearing Lens ..... Steven P. Shearing, M.D.
Suturing Techniques ..... C. William Simcoe, M.D.
Panel Discussion

Sunday, January 14

Symposium: INSTRUMENTS FOR INTRAOCULAR LENS SURGERY
Robert F. Azar, M.D., Moderator
Participants: John Sheets, M.D., Henry Hirschman, M.D., and William Harris, M.D.

Symposium: COMPLICATIONS ASSOCIATED WITH VARIOUS INTRAOCULAR LENSES
Richard P. Kratz, M.D., Moderator
Other Participants to be Announced

Symposium: INTRAOCULAR LENS REMOVAL
Henry Hirschman, M.D., Moderator
Other Participants to be Announced

Symposium: SECONDARY LENS IMPLANTATION
Jerald L. Tennant, M.D., Moderator
Other Participants to be Announced

BASIC COURSE • Saturday, January 13 • 2:00 p.m. to 5:00 p.m.

SOFT CONTACT LENS FITTING FOR OPHTHALMIC ASSISTANTS
Harold A. Stein, M.D., Program Director
Bernard J. Slatt, M.D., Assistant Program Director
Ms Penny Cook and Mrs. Malja Kaufman, Program Coordinators

Terminology
Anatomy of the Cornea
Practical Corneal Physiology
Clinical Selection and Evaluation of Patients
Taking Patient Measurements
Evaluating Lens Parameters
Care and Handling of Soft Lenses
Insertion and Removal Techniques
Selecting the Right Lens
Assessing the Fit
Soft Lens Problems and Solutions
Inventory vs. Per Case Method
Office Practice Management

CLAO MID-WINTER NATIONAL MEETING

This Continuing Medical Education offering meets the criteria for 16 hours credit, Category I of the American Medical Association

Oliver H. Dabezies, Jr., M.D.
Chairman, Mid-Winter Meeting

G. Peter Halberg, M.D., F.A.C.S.
Meeting Secretary

Jack Hartstein, M.D.
President, CLAO

Contact Lens Courses will be held Friday afternoon. You may pre-register for the courses by mail.

Free Papers on contact lenses and intraocular lenses accepted. Please send abstracts to: Oliver H. Dabezies, Jr., M.D., Executive Vice President, CLAO, 2620 Jena Street, New Orleans, Louisiana 70115.

CLAO Annual Business Meeting will be held on Friday, January 12, 1979.

Wine Tasting Party (Friday, January 12) - Sponsored by Barnes-Hind Pharmaceuticals

International Party (Saturday, January 13) - Sponsored by Burton, Parsons & Co.

A special room rate of $34.00 per day (single or double occupancy) has been arranged with the Sahara Hotel. For room reservations only, write the Sahara Hotel, Las Vegas, NV 89114.

PRE-REGISTRATION – CLAO MID-WINTER NATIONAL MEETING

Name _____

Address _____

City _____ State _____ Zip _____

Immediately preceding the scientific session, an optional Practice Management Seminar will be conducted on Thursday, January 11, 1979. There is no registration fee for the Practice Management Seminar. The registration fee for the Scientific Session is the total fee for all sessions.

Registration for the Scientific Session will take place on Wednesday, January 10 from 6:00 p.m. to 8:30 p.m. and Thursday, January 11 from 8:00 a.m. to 5:30 p.m.

☐ Physician Member of CLAO ($200.00)
☐ Physician Non-Member ($250.00)
☐ Resident Physician in Ophthalmology ($150.00)
☐ Technician Employed by Ophthalmologist. Must be identified by letter from the employing ophthalmologist ($175.00)
☐ All Other ($275.00)

Please make check payable to: CLAO Mid-Winter Seminar
and forward to: Paul R. Honan, M.D.
Treasurer, CLAO
P. O. Box 588
Lebanon, Indiana 46052

1979
INTERNATIONAL CATARACT SURGERY SYMPOSIUM

February 5, 6, 7

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FACULTY

D. Peter Choyce *England*	M. U. Dardenne *Germany*	Marvin L. Kwitko *Canada*
Michael Blumenthal *Israel*	Richard P. Kratz *United States*	Donald L. Praeger *United States*
John H. Sheets *United States*	Robert M. Sinsky *United States*	Ronald W. Barnet *United States*

Each member of the faculty will describe his own methods of cataract surgery - with and without lens implants - and management of complications.

Mr. Choyce will give a special presentation about his work with Keratoprotheses.

LECTURES AND WORKSHOPS

- When is intracapsular extraction preferred to extracapsular.
- When are angle supported lenses preferred.
- What is the status of posterior chamber lenses.
- What is the role of A-scan biometry.
- What is the treatment for cystoid macular edema.
- Does the Choyce MK IX lens make the MK VIII obsolete.

This symposium is designed to coordinate with "Frontiers of Ophthalmology" February 8, 9, 10. Physicians may attend both meetings and receive 36 hours CME credit.

For further information, write: Frances Gould, Symposium Coordinator
AFORE
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NEW ORLEANS ACADEMY OF OPHTHALMOLOGY
28th ANNUAL SYMPOSIUM ON
MEDICAL AND SURGICAL DISEASES OF THE CORNEA

March 31—April 4, 1979

HYATT REGENCY NEW ORLEANS • NEW ORLEANS, LOUISIANA

GUEST SPEAKERS

JOSE I. BARRAQUER, M.D.
Refractive Keratoplasty: Indications, Contraindictions, Complications, Results and Technics
Etiopathology of the pterygium

PERRY S. BINDER, M.D.
Corneal Graft Preservation
Corneal Anatomy, Physiology, and Wound Healing
Contact lenses and Orthokeratology

JORGE N. BUXTON, M.D.
Visual Rehabilitation
Keratoconus
Special Corneal Problems

MAX FINE, M.D.
Technics in Phakia and Pseudophakia
Corneal Regrafts
The Recurrent Pterygium:
Mucous Membrane Grafts

RICHARD TROUTMAN, M.D.
Refractive Keratoplasty in the U.S.A.
Effects of Disparate Sized Graft to Recipient Opening
Combined Keratoplasty Technics

DAN B. JONES, M.D.
Inflammatory Diseases of the Lid
Bacterial, Fungal and Visual Keratitis
Therapy of Corneal Perforation

PETER R. LAIBSON, M.D.
The Dry Eye
Herpes Simplex
Corneal Dystrophy—Anterior, Stromal, and Endothelial

ANTHONY B. NESBURN, M.D.
Herpes Simplex and Its Therapy
Recurrent Herpes: Etiology and Pathology
Permanent Wear Contacts

DAVID PATON, M.D.
Penetrating Keratoplasty—Indications, Technics
Contact Lenses and Keratoplasty
Eccentric Tectonic Lamellar Grafts

HYATT REGENCY NEW ORLEANS
Registration—8:30 a.m., Saturday, March 31
Pre-registration packets available 6:00-8:00 p.m. Fri., March 30

SOCIAL EVENTS AND LADIES' TOURS PLANNED

REGISTRATION FEE:
$250.00 Practicing Ophthalmologists, $75.00 Residents Outside Louisiana
Accompanied by letter of identification from Chief of Service

CANCELLATION FEE:
$25.00 after February 1, 1979

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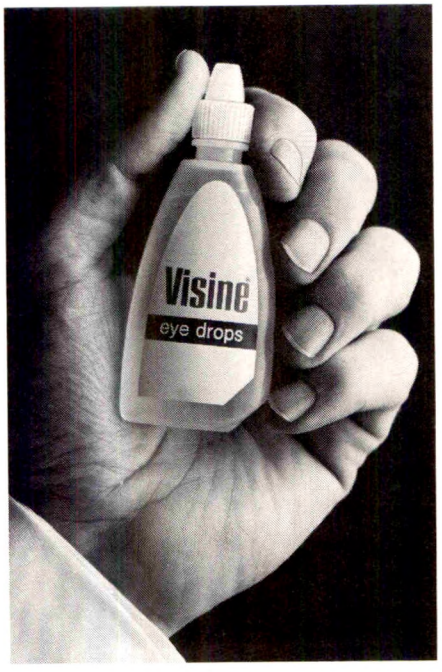
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NATIONAL SPRING MEETING at

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APRIL 22-25, 1979

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Kenneth J. Hoffer, M.D., Santa Monica, California
Charles D. Kelman, M.D., New York, New York
Robert Machemer, M.D., Miami, Florida
Richard C. Troutman, M.D., New York, New York

Otolaryngology Speakers:
Thomas C. Calcaterra, M.D., Los Angeles, California
Michael E. Glasscock, M.D., Nashville, Tennessee
Charles J. Krause, M.D., Iowa City, Iowa
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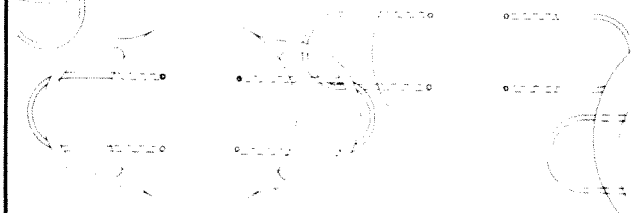
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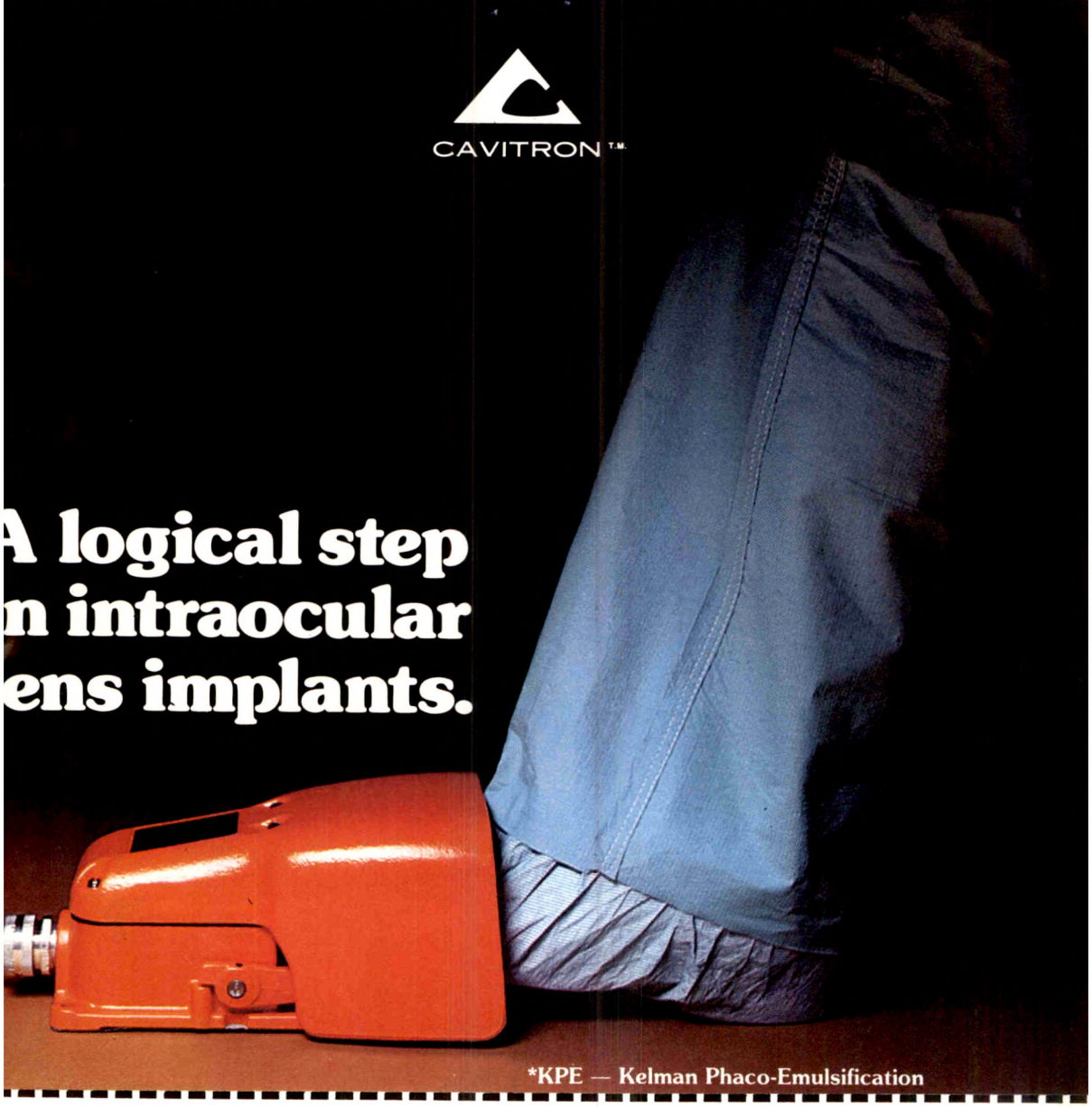
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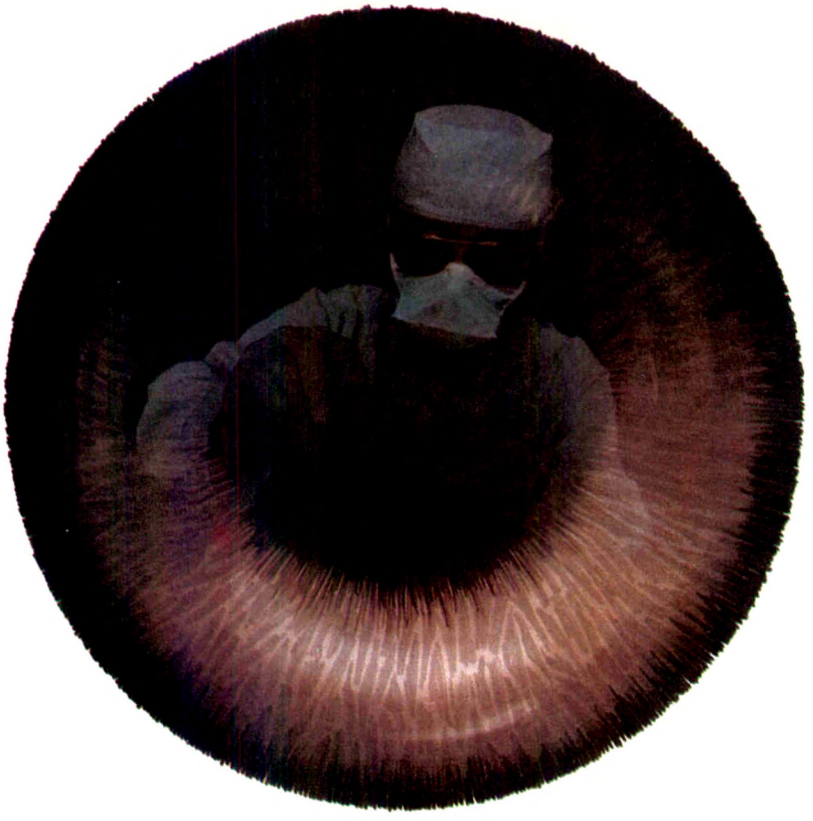
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REFERENCES:

1. Castroviejo, Ramon. The control of postoperative inflammation with fluorometholone. Klin Mbl Augenheilk 166:518-520, 1975.
2. Marun, Edgard. Evaluation of a new topical steroid. Fluorometholone, in the postoperative course of the cataract operation. Ann Ophthal 7:139-142, 1975.

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AMERICAN JOURNAL OF OPHTHALMOLOGY
VOLUME 86 NUMBER 5 NOVEMBER, 1978

HISTOCOMPATIBILITY (HLA) ANTIGENS AND KERATOPLASTY

WALTER J. STARK, M.D., HUGH R. TAYLOR, M.D., WILMA B. BIAS, PH.D., AND A. EDWARD MAUMENEE, M.D.
Baltimore, Maryland

Allograft rejection occurs in about 10% of keratoplasty cases if the recipient cornea is avascular.[1-3] However, if the preoperative corneal bed is densely vascularized, rejection can lead to graft failure in up to 65% of cases.[1,4] The exact role of donor-recipient histocompatibility (HLA) antigens in rejection after keratoplasty is not yet certain. In these high-risk cases of vascularized corneas, some have found a significant correlation between the number of donor and recipient HLA antigens matched and the graft outcome,[4,5] whereas others have not.[6]

The HLA antigen system is the major transplantation antigen system in man as indicated by analysis of familial renal transplantation results.[7,8] Because of the complexity of the HLA antigen system, the probability for complete matching of donor and recipient antigens for unrelated, cadaver transplants is low. In renal transplantation, preimmunization of the recipient to HLA antigens of the donor increases the risk of rejection.[9-13] However, for keratoplasty, the effect of recipient preimmunization has not been fully evaluated.

Patients can become immunized and develop lymphocytotoxic antibodies by exposure to foreign HLA antigens from previous transplants, including corneal transplants,[14] blood transfusions,[10] or pregnancy.[15] Preimmunization of the recipient to antigens of the donor may be detected by preoperative cross-match testing between the recipient's serum and the donor's lymphocytes.[13,16] A negative cross-match test indicates that the recipient has no circulating lymphocytotoxic antibodies specific for the antigens of the donor, whereas a positive cross-match test indicates that the recipient has previously been sensitized and developed antibodies to one or more antigens of the donor. A positive donor-recipient cross-match before renal transplantation almost always results in hyperacute allograft rejection.[13,16]

We report herein our results of penetrating keratoplasty in 84 potentially preimmunized recipients with severe preoperative corneal vascularization. The donor corneas that were used for these patients were selected on the basis of obtaining a negative donor-recipient cross-match test before surgery. No attempt was made to match donor and recipient HLA antigens specifically.

MATERIAL AND METHODS

Eighty-four penetrating keratoplasties were performed between November 1973 and November 1977. Patients selected for

From the Wilmer Ophthalmological Institute (Drs. Stark, Taylor, and Maumenee), and the Immunogenetics Laboratory (Dr. Bias) of the Johns Hopkins Hospital, Baltimore, Maryland. This work was supported in part by Grant EY01302 from the National Eye Institute (Dr. Stark).

Reprint requests to Walter J. Stark, M.D., Wilmer Institute, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21205.

this study had significant vascularization of the corneal stroma in at least three quadrants, extending into the visual axis. Of the 84 patients studied, 64 (76%) had previously had at least one corneal transplant failure in that same eye. These 64 patients had an average of 1.9 previous graft failures, with a range of from one to six previous graft failures in that eye. The remaining 20 patients had previously been exposed to foreign HLA antigens by keratoplasty in the other eye, or by blood transfusion or pregnancy. Of the 84 patients 50 were female and 34 were male. The age of recipients ranged from 13 to 80 years (mean, 60 years). The original diagnosis before the first graft in the eyes studied included: vascularized corneal scars, 31 eyes; corneal edema, 17 eyes; corneal dystrophies, ten eyes; alkali burns, eight eyes; and vascularized corneas of unknown cause, 14 eyes.

Preoperative serum from each recipient was screened for lymphocytotoxic antibodies against a standard panel of lymphocytes from 50 selected donors that, collectively, had all of the known HLA antigens. Each serum was tested against the 50 samples of lymphocytes in the standard donor panel by the microlymphocytotoxicity test,[17] which was performed as follows: crossmatch trays of sera from all patients awaiting corneal grafts were prepared and stored at −80°C. This was done by placing 1μl of each serum in a well of a microtest tray that contained 1 μl of mineral oil. The trays also included positive and negative control sera. These prepared trays were tested against the standard panel of lymphocytes and against corneal donor lymphocytes by adding 1 μl of 1×10^6 cells/ml of lymphocyte suspension to each well. Cells and antisera were incubated for 30 minutes at room temperature. After incubation, excess antibody was washed from the well by adding 10 μl of barbital buffer, allowing cells to settle, and "flicking" buffer from the wells. Four microliters of previously titered rabbit complement was added to each well, and incubation was continued for one hour. Trypan blue was then added to stain cells that were killed in the cytotoxic reaction. Reactions were determined microscopically, and greater than 20% cell death was considered a positive reaction. Cytotoxic reactivity of a recipient's serum against 2% or more of the 50 samples in the panel of donor lymphocytes was considered a significant antibody level. A patient's serum with less than 2% reactivity against the standard panel was determined as having no significant amount of detectable lymphocytotoxic antibody.

Preoperatively, sera from all keratoplasty patients were cross-matched individually against lymphocytes of all the potential corneal donors, as described for the microlymphocytotoxicity test. A specific donor cornea for an individual recipient was selected on the basis of a negative cross-match reaction with the donor's lymphocytes. If a positive cross-match was obtained, the cornea was not used for that recipient. Several of the potentially preimmunized recipients, who had no significantly detectable lymphocytotoxic antibodies on the 50-sample screening tests against our standard panel, still showed a positive cross-match reaction against lymphocytes from some of the potential corneal donors. Therefore, the sera of all of the keratoplasty patients were added to the crossmatch trays regardless of whether they appeared to have antibodies by panel screening. Additionally, HLA typing of both donor and recipient was obtained, but no attempt was made to match donor and recipient antigens specifically.

Donor material for these 84 cases was stored in McCarey-Kaufman medium[18] until used for keratoplasty. Surgery was performed within 60 hours of the donor's death. All grafts were sutured with 10-0

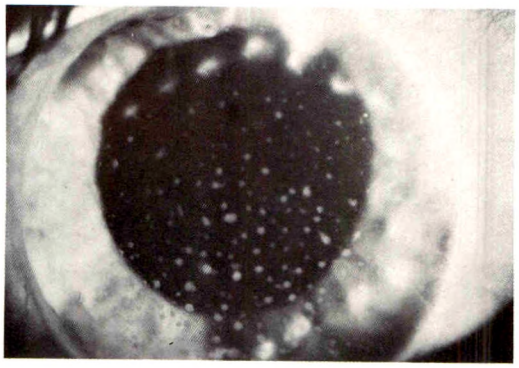


Fig. 1 (Stark and associates). Allograft reaction: keratic precipitates on endothelium of donor cornea.

monofilament nylon suture.[2] Of the 84 grafts, 70 were 7.5 mm in diameter, ten were 8.0 mm in diameter, and four were 7.0 mm in diameter. Forty-four grafts were performed on phakic eyes, and 19 of these were combined with lens removal. The remaining 40 grafts were performed on aphakic eyes.

The diagnosis of immune graft rejection was made only if the graft remained clear for at least two weeks after surgery, and then developed edema or clouding associated with keratic precipitates on the graft endothelium or a rejection line (Figs. 1 and 2). Nonimmune causes of graft failure included grafts that clouded within two weeks of surgery, or graft clouding associated with infection, trauma, glaucoma or persistent epithelial defects with exposure keratitis.

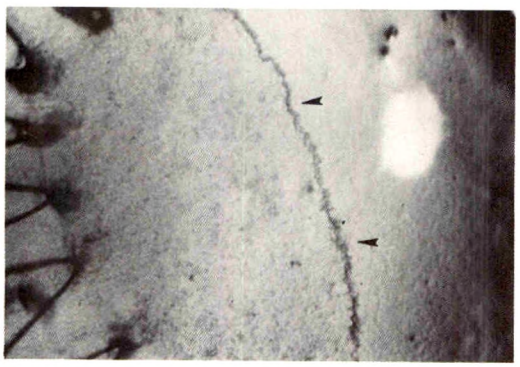


Fig. 2 (Stark and associates). Allograft rejection: rejection line on endothelial surface of donor cornea (arrows denote advancing edge of rejection line).

Results

Negative donor-recipient cross-match pairs—Postoperatively 65 of the 84 corneal grafts (77%) were clear (Figs. 3-5) with an average follow-up of 14.3 months (3 to 45 months). Of the grafts, 15% (13 of 84) have failed from immune allograft rejection, and 7% have failed from causes other than rejection (Table 1). Of graft failures from rejection, 92% (12 of 13) occurred within six months of surgery, with the average time for occurrence of rejection being 3.6 months. Of the 84 patients, 22 (26%) had evidence of an immune event, either rejection or a reversible allograft reaction. Of the 22 immune events, nine (41%) could be reversed with corticosteroids, and 13 (59%) of the cases progressed to graft clouding (Table 2).

The incidence of allograft rejection or the reversibility of an immune event did not differ in those with positive preoperative lymphocytotoxic antibody reactivity of greater than or equal to 2% and those without detectable antibodies (Tables 1 and 2).

The incidence of graft rejection is compared with the number of previous grafts in the same eye in Table 3. A trend exists for an increased risk of rejection with a greater number of previous grafts. A similar trend is seen with the total number of immune events (Table 4), although there is no difference in reversibility of these immune events.

In 84 keratoplasty cases with dense corneal vascularization, our incidence of graft rejection, which was 15%, is less than that reported in similar high-risk cases. Khodadoust[1] reported graft failure from rejection in 65% of cases with dense corneal vascularization, and Batchelor and co-workers[4] reported 60% of such cases with graft failure from rejection.

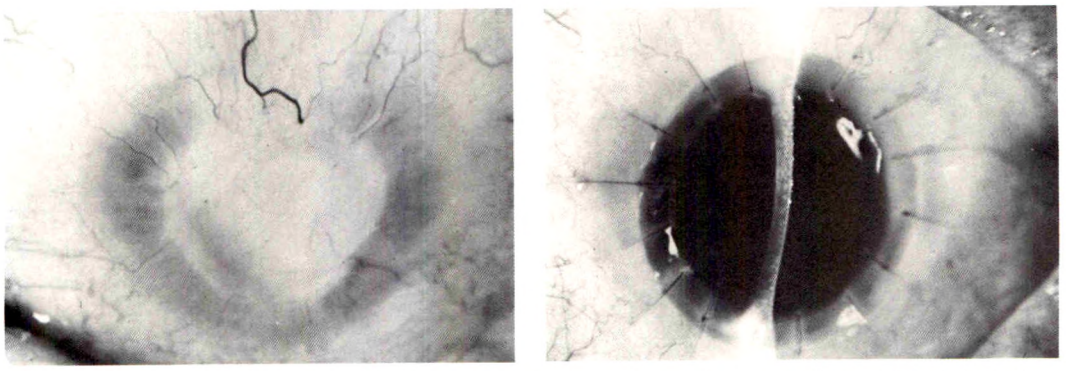


Fig. 3 (Stark and associates). Left, Preoperative appearance of eye after 3 corneal transplant failures from rejection. Right, Postoperative appearance of same eye ten months after keratoplasty. Graft is clear with no evidence of rejection.

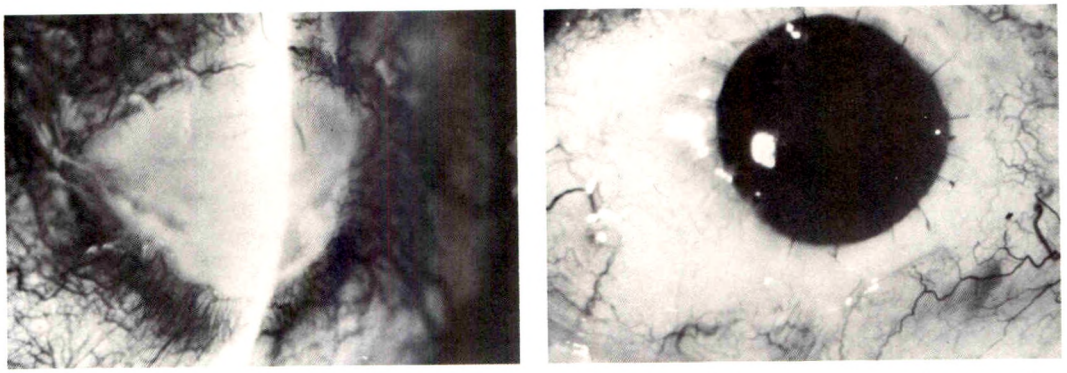


Fig. 4 (Stark and associates). Left, Preoperative appearance of eye with dense corneal vascularization after two previous graft failures. Right, Postoperative appearance of same eye 9 months after keratoplasty with no evidence of rejection.

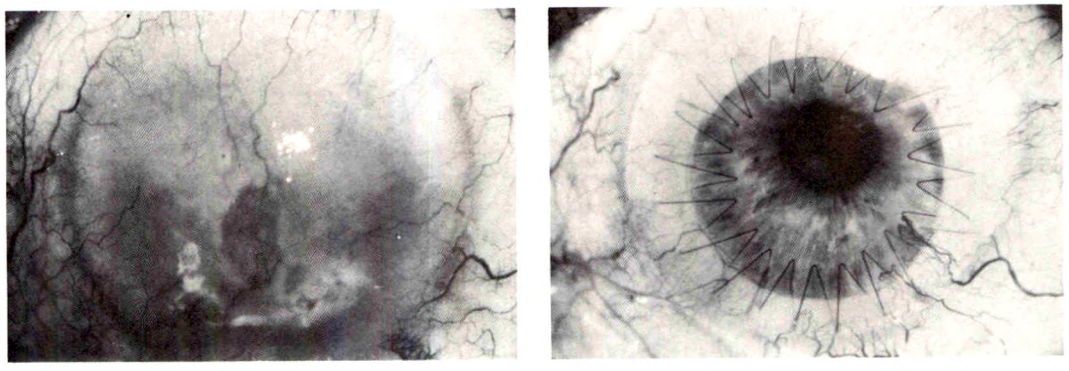


Fig. 5 (Stark and associates). Left, Preoperative appearance of eye with 4+ corneal vascularization. Other eye was lost from complications after keratoplasty. Right, Postoperative appearance of same eye. Vessels are surrounding graft but there is no evidence of rejection 12 months after keratoplasty.

TABLE 1

OUTCOME OF KERATOPLASTY IN POTENTIALLY PRE-IMMUNIZED RECIPIENTS WITH DENSE CORNEAL VASCULARIZATION*

Recipient Preoperative Lymphocytotoxic Antibody Screening Level	Number of Patients				
	Total	Allograft Rejection	Non-Immune Graft Failure	Total Clear	Mean Follow-up (range-mos)
≥2%	48	6(13%)	4(8%)	38(79%)	14.0(3–40)
<2%	36	7(19%)	2(6%)	27(75%)	14.9(3–45)
Total	84	13(15%)	6(7%)	65(77%)	14.3(3–45)

*Negative donor-recipient cross-match.

Although there may have been differences between their series and ours, such as the quality of donor material or patient follow-up availability, these factors are unlikely to account for all of the large differences in incidence of rejection failures between those series and ours. A major cause of the lower incidence of rejection in our series is probably the use of negatively cross-matched donor material. These findings for keratoplasty are in agreement with the results in other tissue and organ transplantation systems.[13,16]

Retrospective donor-recipient HLA antigen matching—The donor and recipient HLA typing results were known for the 84 patients who received negative cross-matched grafts. There were 19 additional patients for whom the donor and recipient HLA types were known. These additional 19 patients also had dense corneal vascularization, but the cross-match test had not been performed. The donor-recipient HLA antigen matching was analyzed retrospectively for these 103 patients.

The occurrence of graft rejection was compared with the number of matching donor and recipient antigens (Table 5). When the donor and recipient shared no matching antigens, rejection failures occurred in 14% of the cases (7 of 51). When one matching antigen was shared, rejection developed in 18% of the cases (6 of 34). In 11 cases in which the donor and recipient shared two matching antigens, there were no graft failures from rejection. However, rejection accounted for failure in two of five cases (40%) in which three matching antigens were shared. In

TABLE 2

IMMUNE REACTIONS IN POTENTIALLY PRE-IMMUNIZED RECIPIENTS WITH DENSE CORNEAL VASCULARIZATION

Recipient Preoperative Lymphocytotoxic Antibody Screening Level	Total Number of Grafts	Total Number of Immune Events (Rejection or Reaction)	Allograft Reaction (Graft Clear)	Percentage Reversed
≥2%	48	9(19%)	3	33
<2%	36	13(36%)	6	46
Total	84	22(26%)	9	41

TABLE 3

COMPARISON OF NUMBER OF PREVIOUS GRAFTS IN OPERATED EYE AND OUTCOME OF KERATOPLASTY IN POTENTIALLY PRE-IMMUNIZED RECIPIENTS WITH DENSE CORNEAL VASCULARIZATION*

Number of Previous Grafts	Number of Patients			
	Total	Allograft Rejection	Non-Immune Graft Failure	Total Clear
0	20	1(5%)	2	17
1	24	3(13%)	2	19
2	28	5(18%)	2	21
3–6	12	4(25%)	0	8

*Negative donor-recipient cross-match.

one case the donor and recipient shared four matching antigens, and this graft was clear.

The incidence of graft failure from rejection does not correlate with the number of matching HLA antigens shared between the donor and recipient. Also, the incidence of immune events and the reversibility of allograft reaction did not correlate with the number of antigens shared (Table 6).

Batchelor and co-workers[4] have the largest series published to date regarding donor-recipient HLA antigen matching and the graft outcome. Seventy-three keratoplasty recipients with dense corneal vascularization showed a reduction in graft failure from rejection as the donor and recipients shared increasingly more matched antigens. Our work does not confirm this in similar high-risk cases (Fig. 6). However, most of our patients received corneas from negatively cross-matched donors. Batchelor and co-workers[4] did not report having used cross-match testing for donor selection, although the probability of negative cross-matches will be higher with donor-recipient pairs that are well-matched for specific antigens. Vannas and co-workers[5] prospectively matched donor and recipient antigens and obtained a negative donor-recipient cross-match test in 18 keratoplasty cases with all degrees of corneal vascularization. Their cases showed a lower incidence of rejection as the num-

TABLE 4

COMPARISON OF NUMBER OF PREVIOUS GRAFTS IN OPERATED EYE AND IMMUNE REACTIONS IN POTENTIALLY PRE-IMMUNIZED RECIPIENTS WITH DENSE CORNEAL VASCULARIZATION

Number of Previous Grafts	Total Number of Grafts	Total Number of Immune Events (Rejection or Reaction)	Allograft Reaction (Graft Clear)	Percentage Reversed
0	20	2	1	50
1	24	5	2	40
2	28	9	4	44
3–6	12	6	2	33

TABLE 5

DONOR-RECIPIENT HLA ANTIGEN MATCHES AND GRAFT OUTCOME

Number of HLA Antigens Matched	Number of Patients	Allograft Rejection	Nonimmune Graft Failure	Clear Graft
0	51	7(14%)	5(10%)	39(76%)
1	35	6(17%)	1(3%)	28(80%)
2	11	0	0	11(100%)
3	5	2(40%)	0	3(60%)
4	1	0	0	1(100%)
Total	103	15(15%)	6(6%)	82(80%)

ber of matched donor-recipient antigens increased (Fig. 7). However, Vannas and co-workers' series included cases with any degree of corneal vascularization, and their recipients may not have had as high a risk of graft rejection as those included in our series and those reported by Batchelor and co-workers.[4]

DISCUSSION

The role of humoral immunity in corneal graft rejection is unknown. Previous work suggests that corneal graft rejection is mediated by cellular immune responses.[19] However, the HLA serologic reactions can be used as indicators of recipient preimmunization, because the major gene loci controlling cell-mediated responses also map within the HLA complex. Thus far, about ten loci, all controlling some aspect of immune function, have been assigned to the HLA region of chromosome 6 in man (Fig. 8).[20] The D locus (or subregion) controls mixed lymphocyte responsiveness, and is an in vitro indicator of cellular immune responsiveness. The entire HLA complex occupies a small segment of the chromosomal length, allowing identification of a given haplotype (the gene complex on one chromosome of the pair) by the serologic specificities it contains.

Our results indicated a lower incidence of corneal graft failure from rejection when cross-match testing was used for donor selection than did other series involving similar high-risk cases with dense corneal vascularization.[1,4] We believe this difference is due mainly to our use of preoperative donor-recipient cross-match testing as a means for donor selection. Thus, we are able to avoid giving a donor

TABLE 6

DONOR-RECIPIENT HLA ANTIGEN MATCH AND GRAFT OUTCOME

Number of HLA Antigens Matched	Number of Patients	Total Number of Immune Events (Reaction or Rejection)	Allograft Reaction (Graft Clear)	Percent Reversed
0	51	14(27%)	7	50
1	35	9(26%)	3	33
2	11	1(9%)	1	100
3	5	2(40%)	0	0
4	1	0	0	—
Total	103	26(25%)	11	42

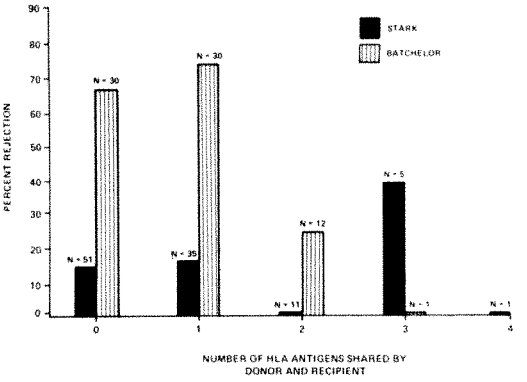


Fig. 6 (Stark and associates). The incidence of rejection after keratoplasty in recipients who have shared zero, one, two, three or four HLA antigens with their donor. Comparison between this study and that of Batchelor and co-workers.[4]

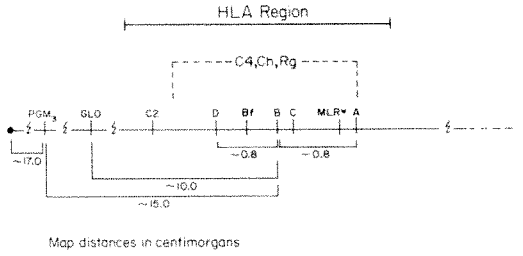


Fig. 8 (Stark and associates). Map of HLA region of chromosome 6.

cornea to a recipient who is presensitized to that cornea's antigens.[21]

Although we found no consistent correlation between the number of matching HLA antigens shared between the donor and recipient and graft outcome, the role of antigen matching deserves further evaluation. However, if further attempts at donor-recipient HLA antigen matching are made, they must be combined with preoperative cross-match testing, because even if all but one of the known donor-recipient antigens are favorably matched, the recipient may still be preimmunized to the one unmatched donor antigen or to unrecognized donor HLA antigens. Although perfect donor-recipient HLA matching for corneal transplantation may be beneficial, it is not currently practical because of the complexity of the HLA system (Table 7).[22] Our study indicates that the use of cross-matching to avoid donors with transplantation antigens to which the recipient is immunized is feasible and seems beneficial.

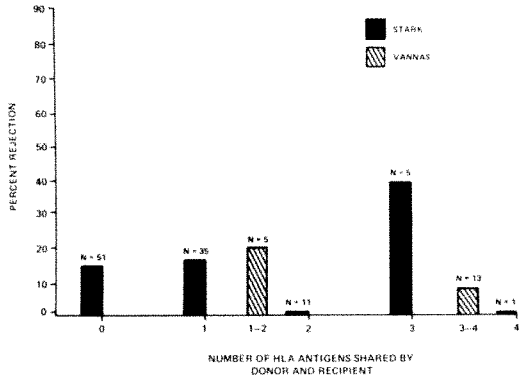


Fig. 7 (Stark and associates). The incidence of rejection after keratoplasty and the number of HLA antigens shared by recipient and donor. Comparison between this study and that of Vannas and co-workers.[5]

We do not have positive donor-recipient cross-match controls, and we therefore consider this to be a prelimiary report. A well-controlled clinical trial is necessary to evaluate fully the results of preoperative donor-recipient cross-match testing for donor selection in keratoplasty, and such a study is currently underway. If controlled studies continue to show a significant beneficial effect from using cross-match testing in high-risk cases for keratoplasty, then this procedure could easily be coordinated with kidney transplant projects without the need for additional expensive equipment and personnel.

SUMMARY

In 84 cases of keratoplasty, all patients had densely vascularized corneas and a history of prior exposure to HLA antigens by pregnancy, blood transfusion, or previous transplantation. Donors were selected on the basis of a negative cross-

TABLE 7

LISTING OF RECOGNIZED HLA SPECIFICITIES(1978)

A Locus	B Locus	C Locus	D Locus
HLA—A1	HLA—B5	HLA—CW1	HLA—DW1
HLA—A2	HLA—B7	HLA—CW2	HLA—DW2
HLA—A3	HLA—B8	HLA—CW3	HLA—DW3
HLA—A9	HLA—B12	HLA—CW4	HLA—DW4
HLA—A10	HLA—B13	HLA—CW5	HLA—DW5
HLA—A11	HLA—B14	HLA—CW6	HLA—DW6
HLA—A28	HLA—B15	Blank	HLA—DW7
HLA—A29	HLA—B17		HLA—DW8
HLA—AW23	HLA—B18		HLA—DW9
HLA—AW24	HLA—B27		HLA—DW10
HLA—AW25	HLA—B37		HLA—DW11
HLA—AW26	HLA—BW16		Blank
HLA—AW30	HLA—BW21		
HLA—AW31	HLA—BW22		
HLA—AW32	HLA—BW35		
HLA—AW33	HLA—BW38		
HLA—AW34	HLA—BW39		
HLA—AW36	HLA—BW40		
HLA—AW43	HLA—BW41		
Blank	HLA—BW42		
	HLA—BW44		
	HLA—BW45		
	HLA—BW46		
	HLA—BW47		
	HLA—BW48		
	HLA—BW49		
	HLA—BW50		
	HLA—BW51		
	HLA—BW52		
	HLA—BW53		
	HLA—BW54		
	Blank		

match to avoid donor antigens to which the recipient was preimmunized. The overall rate of graft failure from rejection was 15%. A retrospective analysis of donor-recipient HLA matching in 103 high-risk cases showed no consistent correlation between the number of antigens shared and graft outcome. These findings indicated negative cross-match to be important in donor selection for keratoplasty in high-risk cases.

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CORNEAL DONOR MATERIAL SELECTION

Z. NICHOLAS ZAKOV, M.D., CLAES H. DOHLMAN, M.D.,
HENRY D. PERRY, M.D., AND DANIEL M. ALBERT, M.D.

Boston, Massachusetts

An important responsibility of the corneal surgeon is to evaluate corneal donor material. The chief concern has been with extending the viability and assessing the health of the endothelium. Little has been said about exclusion of donor material because of cause of death, with the exception of Creutzfeldt-Jakob disease. This neurologic disorder, which has been transferred by keratoplasty, emphasizes the importance of the cause of death. No uniform code of exclusion of donor material by disease entity exists.

Ophthalmic pathologists contribute to the solution of this problem by making histopathologic observations not obvious to the corneal surgeon. Ophthalmic pathologists must examine the globes used for corneal donor material. In reviewing such material after the fact and in a different context from the surgeon, concern regarding the possible hazards involved with certain donor material is evident. We report herein three cases in which donor eyes illustrate the need for a reevaluation of the criteria used in selecting donor corneal material, and a standardization of those criteria.

CASE REPORTS

Case 1—The donor cornea was obtained from a 49-year-old patient who died of acute leukemia. Histopathologic examination of the donor eye after the removal of the corneal button revealed the following positive findings: thickening and posterior migration of the lens epithelium; gliotic and thickened retina, especially in the macular area, with microcystoid degeneration peripherally. The choroid was diffusely infiltrated by a large number of immature white cells, which were variable in size and had large basophilic nuclei with prominent nucleoli and irregular chromatin clumping. These were evident within blood vessels and extravascularly. The optic nerve showed thickened septa with mild gliosis. Examination of the fellow eye showed a similar histopathologic picture, and additionally, showed leukemic keratitic precipitates on the corneal endothelium. The eye that was used for the donor cornea was chosen arbitrarily and the keratitic precipitates in the fellow eye were not noted on preoperative screening of the donor material. Other eye bank eyes with massive leukemic infiltrates (Fig. 1) have subsequently been observed by us.

Case 2—The donor cornea was obtained from a patient who died of glioblastoma multiforme and had had mitral valve disease. There was also a history of rash and fever. The right fundus examination showed two brown, granular-appearing lesions along the inferior nasal vessels. The left fundus had flame-shaped hemorrhages. The diagnosis of subacute bacterial endocarditis in addition to the brain tumor had been considered before death, but not verified. At autopsy, heart valve cultures grew the following organisms: *Staphylococcus aureus, S. enterococci, Klebsiella pneumoniae,* and *K. lactobacilli.*

Histopathologic examination of the donor eye revealed inflammatory nodules in the ciliary body and the choroid with some central necrosis (Fig. 2, left). These microabscesses were localized and were composed of acute and chronic inflammatory cells, predominantly lymphocytes and macrophages (Fig. 2, right). Clusters of gram-positive bacteria were also present. In the midperipheral area, an abscess had focally destroyed and disrupted the retinal elements through a break in Bruch's membrane, and there were inflammatory cells in the overlying vitreous.

Case 3—The donor cornea was obtained from a patient with known metastatic breast carcinoma. Examination of the donor eyes showed that the left eye was entirely normal except for missing cornea, iris, and part of the ciliary body. In the right eye the cornea, iris, and part of the ciliary body were missing. The choroid contained a focus of invasion by metastatic breast tumor in an "Indian file" fashion. The cells were anaplastic with large vesicular and variable in size nuclei. Some tumor cells contained PAS-positive material. The cell columns extended to the ciliary body (Fig. 3) and adjacent to the wound area where the anterior segment structures were removed for transplant.

In all cases no adverse ocular effects or systemic

From the Howe Laboratory of Ophthalmology, Massachusetts Eye and Ear Infirmary (Drs. Zakov, Dohlman, and Albert), Boston, Massachusetts, and the Walson Army Hospital, Department of Ophthalmology (Dr. Perry), Fort Dix, New Jersey.

Reprint requests to Daniel M. Albert, M.D., Howe Laboratory of Ophthalmology, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114.

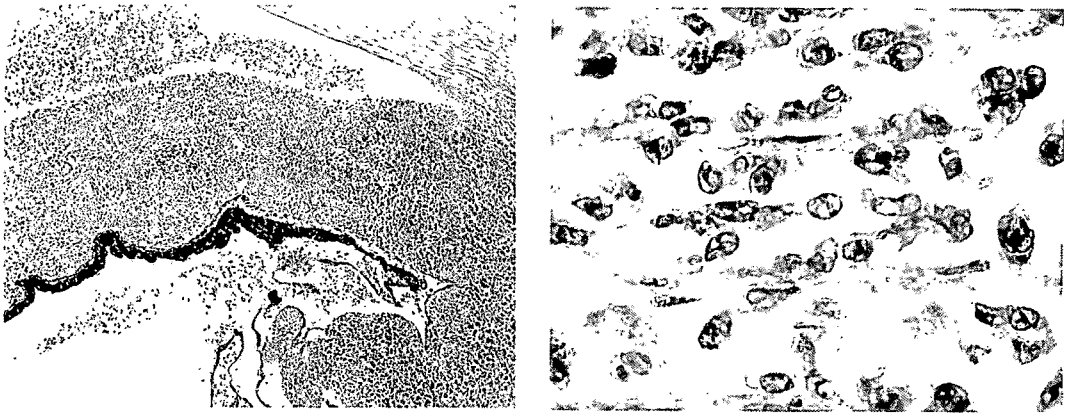


Fig. 1 (Zakov and associates). Left, Example of an eye bank eye showing massive infiltration of iris with leukemic cells (hematoxylin and eosin, ×50). Right, Higher power showing leukemic cells (heratoxylin and eosin, ×1040).

complications have occurred to the recipients to date (postoperative duration, seven months to two years).

Discussion

There are few commonly accepted standards for selection of corneal donor material among surgeons. The criteria for exclusion of donor material are variable. A survey of eye bank procedures carried out by Rabb and Brose[1] showed a wide range of conditions mentioned, rendering the donor material unacceptable for transplantation purposes by the various eye banks. However, there was no uniformity in adhering to this exclusion code by the eye banks surveyed.

Case 1 of our series shows that the use of leukemic donor material may lead to the transplantation of viable leukemic cells to the recipient's anterior chamber. It may be argued that the recipient's immune mechanisms will be able to handle the leukemic cell load. However, the etiology of leukemia, and especially its relation to a viral pathogenesis, is not clear. C-type and virus-like particles have been described in human leukemic cells.[2–4] C-type particles have been observed in a variety of other human cancers.[5–9] The Epstein-Barr virus is associated with two human malignancies, Burkitt's lymphoma and human nasopharyngeal carcino-

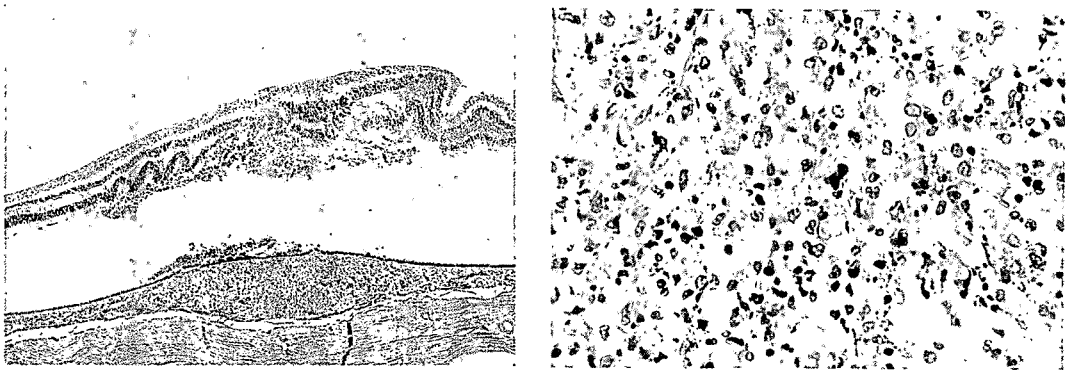


Fig. 2 (Zakov and associates). Left, Retinal and choroidal abcess (PAS, ×30). Right, Primarily mononuclear cells in choroidal abscess (hematoxylin and eosin, ×750).

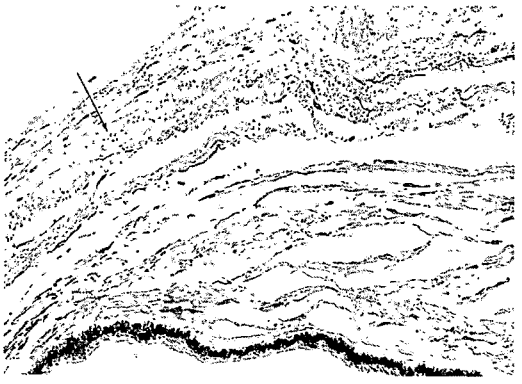


Fig. 3 (Zakov and associates). Ciliary body stroma and muscles infiltrated by metastatic breast carcinoma cells (arrow) in characteristic "Indian file" pattern (hematoxylin and eosin, ×94).

ma. Patients with these tumors always have increased serum titers against Epstein-Barr virus associated antigens, and tumor biopsy specimens from these malignancies grown in athymic nude mice contain Epstein-Barr virus DNA in a covalently closed circular form.

Dohlman and Boruchoff[10] noted that donor material from leukemic patients should be rejected, and they cited a case in which a gliomatous growth occurred in a grafted eye with the donor eye having retinoblastoma. Even though no convincing demonstration of the infectivity of human associated C-type particles in vivo has been shown, no long-range studies on the effect of transplanting tumor cells have been done. No long-range study of corneal transplantation has been done to demonstrate possible negative effects on the recipient who has received material from patients dying with malignancies and various neurologic disorders. This is particularly important since many recipients are young and presumably would have a long period to express any long-term effects of transplantation. In our three cases, all recipients were under age 34 years.

Case 2 emphasizes that sufficient history of the donor material is not always available. Terminal septicemia indicates that the donor material is not suitable for transplant purposes. Pollack[11] noted that donor corneas obtained from debilitated donors or cancer patients treated with immunosuppressive drugs do not survive cryopreservation and do not function as well as healthy donor tissue. Chronically ill patients on long-term corticosteroids, immunosuppressive or multiple antibiotic regimens may harbor occult infection, not apparent on a cursory perusal of the donors' terminal diagnoses. Additionally, a recent study by Keates, Mishler, and Riedinger[12] showed that it is not possible to render donor eyes sterile from patients with systemic infections by using current techniques. Of corneas stored in the McCarey-Kaufman medium, 30% in their study, and 40% of corneas stored in moist chambers had positive cultures. They also were able to isolate organisms from the aqueous of three donor eyes and suggested that this may be a source of contamination to the cornea. In our Case 2 the vitreous abscess present was not noted on screening of the donor eye. Conversely, the risk of postoperative infection in the transplanted eye is small. Recently, cryptococcal endophthalmitis developing after corneal transplantation was reported.[13] The donor material was obtained from a patient with a history of polymyositis who had been treated with corticosteroids and intermittent cyclophosphamide. Additionally, the patient had evidence of *Pneumocystis carinii* and cytomegalovirus infection, and the blood cultures confirmed the presence of *Cryptococcus neoformans* after death. Before keratoplasty, the corneal graft was bathed with a solution of polymyxin B sulfate, neomycin, and gramicidin and stored for 48 hours at 4° C. Routine bacteriologic studies of the aqueous were negative, but the eye was not examined pathologically.

Case 3 emphasizes the concept that

slit-lamp evaluation of the donor material is inadequate in establishing the presence of metastatic disease to the ciliary body in the donor eye. Gross examination of the globe in the eye pathology laboratory failed to raise suspicion of metastatic disease to the globe, and only the histopathologic sections showed tumor in close proximity to the line of resection of the donor corneal button. Although 89% of eye banks queried by Rabb and Brose[1] stated that anterior segment tumors make donor corneas unacceptable for transplant purposes, our Case 3 clearly illustrates that there is no sure method of ruling out this diagnosis short of histopathologic sectioning of the globe.

Transmission of Creutzfeldt-Jakob disease through a corneal transplant has been documented.[14-17] However, recent evidence presented by Gajdusek and associates[18,19] suggests that donor material from aged patients, and particularly patients with any dementia, should not be used for corneal grafting. Accidental transmission of Creutzfeldt-Jakob disease has occurred in two neurosurgic cases through the use of contaminated stereotactic electrodes,[20] and there is suspicion that a neurosurgeon may have contracted the disease from one of his patients.[19] Experimentally, corneas from guinea pigs with Creutzfeldt-Jakob disease, when placed in the anterior chambers of healthy guinea pigs, produced clinical and histologic evidence of Creutzfeldt-Jakob disease in all of the animals after approximately a two-year incubation period.[21] Another feature of Creutzfeldt-Jakob disease, not clearly understood at the present time, is that patients developing it have a higher frequency of having had brain or eye surgery within two years before the onset of the disease.[19] Since the virus responsible for this fatal condition is extremely hardy and resists inactivation even by 10% formalin and 70% alcohol solutions,[19] certain precautions in handling patients with Creutzfeldt-Jakob disease and their tissues become mandatory. Gajdusek and associates[19] recommended that tonometers and surgical instruments used on patients with this disease be properly sterilized. This can be achieved by autoclaving for one hour at 121° C and 20 psi or by the use of 5% hypochlorite, 0.03% permanganate, phenolics and iodine solutions.[19]

The following conditions should render donor material absolutely unacceptable for transplant purposes: Creutzfeldt-Jakob disease, any dementia, and probably any chronic neurologic disorder unless clearly secondary to a traumatic etiology. This includes subacute sclerosing panencephalitis, progressive congenital rubella, progressive multifocal leukoencephalopathy, cytomegalovirus brain infection, Crohn's disease, and subacute encephalitis.[18] Ophthalmologists should also be aware of the many other conditions in which slow virus etiology is suspected, but so far not proven. This includes multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, some of the collagen vascular diseases, and others.[18] Other conditions include: septicemia; hepatitis, jaundice, and evidence of any active viral infection; syphilis and positive serology (in certain cases of treated tertiary syphilis, the cornea is probably noninfectious and safe to use).

Many other conditions require extreme caution with regard to selection as donor material, although currently no statements can be made regarding absolute contraindication to use. These conditions include: (1) ocular or systemic malignancy of any kind; (2) long terminal disease, particularly if immunosuppressive agents, large doses of corticosteroids, and multiple antibiotic regimens were used terminally and particularly if there is evidence of systemic or focal infection; (3)

history of eye diseases, including external eye diseases, corneal disease or dystrophy, iritis, absolute glaucoma, and acute glaucoma attack; and (4) history of previous intraocular surgical procedure of any kind.

The above criteria for selection of donor corneal material are practical and are currently implemented at the New England Eyebank in Boston, Massachusetts.

The majority of corneal grafting procedures are elective by nature. A thorough evaluation of donor material should be undertaken by the corneal surgeon and the eyebanks. In emergencies, use of material from donor eyes with the previously mentioned relative contraindications may be justified. The tightening up of guidelines on the use of donor material should serve as a further impetus for research to achieve more satisfactory ways of preserving donor tissue. From our study, we believe it would be advisable to initiate a long-term prospective study on the effects of keratoplasty in which the clinical and pathologic findings of the donor as well as any ocular or systemic changes of the recipient are recorded.

Summary

Histologic study of eyes used as donor material for corneal transplant revealed one instance of massive leukemic infiltration with leukemic keratic precipitates on the fellow eye. In another eye, microabscesses composed of acute and chronic inflammatory cells containing *Cryptococcus neoformans* were present. In a third patient metastatic anaplastic cells were present in the choroid. We think donor eyes are absolutely unacceptable if death was caused by any chronic neurologic disorder, unless clearly secondary to trauma. Eyes from patients with septecimia, hepatitis, jaundice and any evidence of any active viral infection, syphilis, and positive serology are also unacceptable. Extreme caution should be used in selecting eyes of patients with ocular or systemic malignancy, long-term diseases, particularly if immunosuppressive agents were used, where a history of eye disease exists, including corneal disease or dystrophy, iritis, absolute glaucoma or acute glaucoma, and eyes with a history of previous intraocular surgery.

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PERIPHERAL CORNEAL ULCERS WITH HERPES ZOSTER OPHTHALMICUS

BARTLY J. MONDINO, M.D., STUART I. BROWN, M.D.,
AND
JAMES P. MONDZELEWSKI, M.D.

The corneal manifestations of herpes zoster are diverse and potentially serious. The corneal epithelium may display a coarse punctate keratitis,[1] vesicles,[2] mucus plaques,[3] and dendrites.[2–4] Characteristic subepithelial nummular opacities,[1] irregularly shaped stromal opacities,[1] disciform keratitis,[5] deep sclerosing interstitial keratitis,[6] and ring abscess of the cornea[6] have all been reported with herpes zoster. Corneal involvement in herpes zoster ophthalmicus includes central and paracentral ulcerations which may result in perforation and even sloughing of the entire cornea.[5,7]

We describe herein four patients who developed peripheral ulcerations of the cornea following herpes zoster ophthalmicus. To our knowledge, this association has not been previously reported.

CASE REPORTS

Case 1—A 72-year-old woman developed lesions typical of herpes zoster in the distribution of the ophthalmic division of the fifth cranial nerve on the left in June 1973. A low-grade uveitis with photophobia developed and persisted in the left eye. In February 1974, the patient complained of increasing pain, tearing, and photophobia in both eyes for the past two months. At that time, the visual acuity was R.E.: 6/18 (20/60); L.E.: 6/6 (20/20). Slit-lamp examination disclosed a peripheral corneal ulcer running from the 2 to the 4 o'clock meridian in the right eye with an undermined advancing edge and with heaped up conjunctiva at its posterior border. The left eye also revealed a peripheral ulceration of the cornea running from approximately the 1:30 to the 4:30 meridian. The advancing edge was undermined with infiltrates noted in the leading edge as well as in the base of the ulcer. The peripheral ulcers encircled both corneas and advanced centrally (Fig. 1). Numerous conjunctival excisions adjacent to the ulcers resulted in only transient epithelial healing and relief of pain. Intraocular pressure by pneumotonometry was R.E.: 23 mm Hg; L.E.: 12 mm Hg. Both corneas were eventually destroyed and covered with vascularized conjunctival epithelium.

Case 2—A 60-year-old woman with a 20-year history of diabetes mellitus developed herpes zoster on the right side of her face in the distribution of the ophthalmic division of the fifth cranial nerve in August 1970. An anterior uveitis was noted in the right eye with 1+ flare and cells. During the next week, the anterior chamber reaction increased to 3+ flare and cells, and the cornea developed diffuse punctate staining of the epithelium and stromal edema. While the patient was receiving cycloplegics and topical corticosteroids, the anterior chamber largely cleared, leaving 1+ flare and a few small residual keratic precipitates. The vision at this time was 6/24 (20/80). In April 1971, the anterior uveitis flared up in the right eye with a heavy cell and flare reaction and mutton-fat keratic precipitates. Intraocular pressure by applanation tonometry in the right eye was 22 mm Hg. During the next year, the anterior uveitis flared up on two more occasions, requiring the use of topical and subconjunctival corticosteroids. Except for punctate staining, the cornea was uninvolved. In November 1972, the patient had pain and photophobia in the right eye and recurrent anterior uveitis. Additionally, a peripheral corneal ulceration with a steep central edge was noted in the right eye extending from approximately the 2 o'clock to the 4 o'clock meridian. The



Fig. 1 (Mondino, Brown, and Mondzelewski). Case 1. Left eye with peripheral ulcer extending circumferentially and centripetally.

From the Department of Ophthalmology, University of Pittsburgh School of Medicine and Eye and Ear Hospital. This study was supported in part by National Eye Institute Grant No. 1 RO1 EY02304-01 (Dr. Mondino).

Reprint requests to Bartly J. Mondino, M.D., Department of Ophthalmology, Eye and Ear Hospital, 230 Lothrop St., Pittsburgh, PA 15213.

ulcer extended centrally and peripherally to involve the cornea from the 12 o'clock to the 6 o'clock meridian. After treatment with topical and subconjunctival corticosteroids, the ulcerative process ceased and the eye quieted. Intraocular pressure by applanation tonometry was R.E.: 10 mm Hg; L.E.: 12 mm Hg. The final visual acuity was 6/60 (20/200) with correction.

Case 3—In June 1976, a 59-year-old woman had cervical and inguinal lymphadenopathy and a leukocytosis of 80,000. A diagnosis of chronic lymphocytic leukemia was made. The patient was treated with chlorambucil with a decrease in her lymphadenopathy and white blood cell count.

In October 1977, the patient's lymphadenopathy increased, and she was treated with oral cyclophosphamide and prednisone with some improvement. Two weeks later, the patient developed vesicular-pustular lesions over her left hemifacial area with swelling of her left eyelid. The diagnosis of herpes zoster was made. The lesions spread from her left hemifacial area to her left trunk in a dermatomal distribution. The patient developed severe pain in the left eye and forehead with a fever, confusion, global aphasia, and a right central seventh cranial nerve lesion. Lumbar puncture revealed a cerebrospinal fluid protein of 374, and a diagnosis of herpes zoster encephalitis was made. An ophthalmologic examination in November 1977 revealed normal anterior segments with 6/6 (20/20) vision in both eyes.

In January 1978, the patient complained of deep boring pain in her left retro-orbital area. The skin of the left side of the forehead and the left upper eyelid was thin and scarred. The visual acuity was R.E.: 6/6 (20/20); L.E.: hand movements. The bulbar conjunctiva of the left eye was hyperemic and the corneal sensation was reduced. A vascularized area of corneal thinning with an intact epithelium was noted in the periphery of the cornea from approximately the 7 o'clock to the 10 o'clock meridian. The central edge of this peripheral furrow was steep and elevated (Fig. 2). The corneal endothelium was diffusely covered with medium-sized keratic precipitates. A 1-mm hyphema and 4+ cells and flare with fibrinous strands in the anterior chamber were present. Intraocular pressure by applanation tonometry was R.E.: 10 mm Hg; L.E.: 15 mm Hg. The patient died one month later.

Case 4—A 74-year-old man had bronchogenic adenocarcinoma of the right upper lobe at thoracotomy in June 1971. The tumor was considered unresectable, and radioactive implants were used. Thereafter, the patient was treated with external radiation and chemotherapy with 5-fluorouracil for six months. In May 1972, the patient complained of severe headaches and had signs of cerebral involvement. A brain scan and cerebral arteriogram revealed a solitary frontal metastasis, which was excised during a right frontal craniotomy.

In February 1973, the patient developed herpes zoster in the distribution of the ophthalmic division of the fifth cranial nerve on the right. His visual acuity with correction was R.E.: 6/30 (20/100); L.E. 6/6 (20/20). Corneal sensation was found to be decreased on the right when compared to the left. A varicella-zoster titer rose from 1/16 to 1/1024. The patient was treated with a five-day course of cytosine arabinoside. Shortly thereafter, he became confused and a right sixth nerve paresis was noted. Additionally, the patient developed a peripheral corneal ulcer in his right eye with moderate conjunctival hyperemia and an anterior uveitis. The ulcer involved two thirds of the corneal circumference and was approximately 3 mm wide. The central edge of the ulcer was infiltrated and steep (Fig. 3). Intraocular pressure by palpation was normal. Although *Staphylococcus aureus* was cultured from the eye, the ulcer did not resemble a catarrhal ulcer because of its steep edge and the absence of a lucid interval. The epithelium covered the ulcer in four to five days while the patient was being treated with topical neosporin and oral dicloxacillin (Fig. 4). The patient was also being treated with oral dexamethasone, which resulted in some improvement in his mentation. The patient died in April 1973.

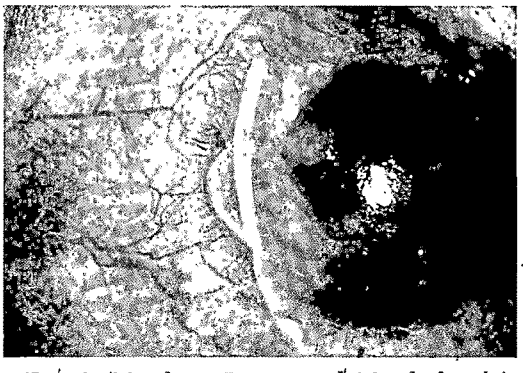


Fig. 2 (Mondino, Brown, and Mondzelewski). Case 3. Peripheral furrow of left eye running from 7 to 10 o'clock.

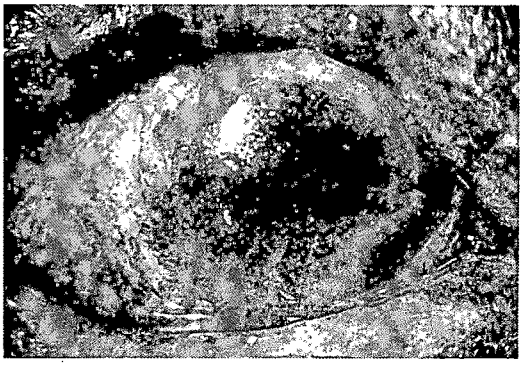


Fig. 3 (Mondino, Brown, and Mondzelewski). Case 4. Peripheral ulcer of right eye involving two thirds of the corneal circumference.



Fig. 4 (Mondino, Brown, and Mondzelewski). Case 4. Healed peripheral furrow.

Discussion

A wide variety of systemic diseases have been associated with peripheral ulcers of the cornea: acute myeloblastic leukemia, acute monocytic leukemia, scleroderma, systemic lupus erythematosus, influenza, bacillary dysentary, polyarteritis nodosa, Wegener's granulomatosis, rheumatoid arthritis, porphyria, gonococcal arthritis, tuberculosis, and brucellosis.[8,9] Peripheral corneal ulcers following routine cataract extractions[10] and following systemic administration of gold[11] have been reported.

In this report, four patients developed peripheral corneal ulcerations with steep central edges following herpes zoster ophthalmicus. An anterior uveitis complicated herpes zoster in all four cases. In Case 1, bilateral peripheral corneal ulcers typical of Mooren's ulcer developed that encircled and eventually destroyed both corneas. In the other three cases, the peripheral corneal ulcers were not relentlessly progressive and were found only on the side of the herpes zoster ophthalmicus. Only the patient in Case 1 was free of systemic disease. The patient in Case 2 had diabetes mellitus, the patient in Case 3 had chronic lymphocytic leukemia, and the patient in Case 4 had bronchogenic carcinoma with widespread metastases.

The pathogenesis and relationship of these peripheral corneal ulcers to herpes zoster ophthalmicus is speculative. The patients in Cases 3 and 4 developed peripheral corneal ulcerations soon after the active skin lesions of herpes zoster. Replicating virus, occlusive vasculitis, and even neurogenic disturbances might be important in the development of peripheral ulcers in these two cases. In Case 4, *S. aureus* was recovered from conjunctival cultures. In this immunosuppressed patient with herpes zoster, an unusual immune response to *Staphylococcus* may have been involved in the development of this peripheral corneal ulcer. The ulcer did not resemble the typical catarrhal ulcer because of its steep central edge and the absence of a lucid interval.

The patients in Cases 1 and 2 developed peripheral corneal ulcers six months and two years, respectively, after the active skin lesions of herpes zoster. In Case 1, however, the peripheral ulcers were preceded by a low-grade uveitis, whereas in Case 2, the peripheral ulcer developed in a setting of recurrent anterior uveitis. A recrudescence of viral replication may be responsible for these lesions, but virus-altered corneal antigen in these patients may have led to the development of autoimmune reactions, which may have been important in the pathogenesis of these ulcers. Cell-mediated autoimmune phenomena have been reported in association with herpes zoster keratitis with patients having positive leukocyte migration inhibition in response to normal corneal antigen.[12] The patient in Case 1 developed a typical Mooren's ulcer, a condition which has been related to antecedent ocular injury[13] and which has been associated with both cellular[14] and humoral autoimmune phenomena.[15]

Summary

Four patients with herpes zoster ophthalmicus developed peripheral corneal

ulcers with steep central edges. An anterior uveitis was associated with all cases. One patient developed bilateral corneal ulcers that were typical of Mooren's ulcer and eventually destroyed both corneas. The other three cases were unilateral and were not relentlessly progressive.

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TOPICAL RETINOIC ACID IN THE TREATMENT OF CORNEAL XEROPHTHALMIA

ALFRED SOMMER, M.D., AND NANI EMRAN, M.D.
Bandung, Indonesia

Xerophthalmia remains the most important cause of childhood blindness in many developing countries. Vitamin A deficiency results in punctate epithelial keratopathy with or without stromal edema (2)[1] and ulceration (×3A).[2] The cause of keratomalacia (×3B) is probably more complex.[2]

It is commonly classified, by WHO criteria, into night blindness (×N), conjunctival xerosis (×1A), conjunctival xerosis with Bitot's spot (×1B, corneal xerosis (×2), corneal xerosis with ulceration (×3A, and keratomalacia (×3B).

The only therapy proven effective for corneal xerophthalmia (×2, ×3A) in humans is systemic vitamin A, administered as retinyl palmitate (or other esters). In the first 50 cases treated on our study ward, however, the clinical response was often delayed one to four days, and the cornea occasionally deteriorated in the interim. As a possible means of bridging this critical period, we have begun trials with topical retinoic acid. Unlike retinyl palmitate, retinoic acid does not require prior de-esterification and may not require conjugation with specific carrier proteins (which are often depressed in malnourished xerophthalmic children) to reach the target cells. Preliminary results indicate topical retinoic acid is a safe and effective means of speeding corneal healing in xerophthalmia.

From the Nutritional Blindness Prevention Project, Bandung Indonesia (Drs. Sommer and Emran), and the Wilmer Institute, Johns Hopkins Hospital, Baltimore, Maryland (Dr. Sommer).

Reprint requests to Alfred Sommer, M.D., P. O. Box 134, Bandung, Indonesia.

SUBJECTS AND METHODS

Since June 1977, 58 xerophthalmic children with classical corneal involvement have been studied on our ward. Each child underwent complete ophthalmologic, pediatric, biochemical, and bacteriologic examination.

At our request, Roche Laboratories prepared sterile single-application vials of 0.1% retinoic acid in arachis oil and placebo delivering 25 μl per drop. Before releasing the retinoic acid and the placebo for use, Roche conducted toxicity trials in their own laboratories. Application to rabbit eyes produced only mild conjunctival injection (W. Hausheer, M.D., and A. Hanck, M.D., personal communication, Dec. 14, 1977).

All eight children in this pilot trial underwent our standard therapeutic regimen: hospitalization, high-protein diet, systemic vitamin A (either 100,000 IU water-miscible vitamin A intramuscularly, or 200,000 IU oil-miscible vitamin A orally on admission, according to a concurrently running protocol, and an additional dose of 200,000 IU orally the following day). Informed consent was provided by the parent or guardian accompanying the child. Only children with intact globes were included in the study. When the two eyes were symmetrically and equally affected, the retinoic acid was applied to the right eye, placebo to the left. In cases of unequal involvement, retinoic acid was placed in the more severely involved eye. Every attempt was made to examine the children daily with the slit lamp.

The first two patients received only a single drop of retinoic acid and placebo

Absence of any signs of toxicity encouraged us to apply an additional drop of each agent the following day. The frequency and amount applied was gradually increased to our present regimen of two drops five times a day, gently blotting any excess off the eyelids to prevent cross contamination.

RESULTS

Eight children have been treated to date, none with any evidence of significant toxicity. Both eyes of one child (Case 2) developed minimal injection at 24 hours, but this cleared spontaneously the following day.

Four children had relatively symmetrical disease in the two eyes. In every instance the eye receiving retinoic acid showed earlier improvement.

CASE REPORTS

Case 1—A 2-year-old severely malnourished (grade 3) Indonesian girl had severe corneal xerosis (×2) bilaterally. There was no evidence of stromal edema. One drop of retinoic acid was placed in the right eye and one drop of placebo in the left eye on admission and daily thereafter. The following day (day two) there was no conjunctival injection, but the corneal xerosis remained unchanged and equal in the two eyes. By day three both eyes showed improvement, the right eye (retinoic acid recipient) more so than the left. By day five the right cornea was completely clear, whereas the left eye still had numerous punctate lesions; a rough, granular surface; and poor wettability (but less than five seconds throughout).

Case 2—A 4-year-old mildly malnourished (grade 1) Indonesian boy had extensive corneal xerosis (×2) bilaterally. Both corneas exhibited moderate diffuse haze to hand-light examination and frank xerotic plaques inferiorly. Minimal stromal edema was present inferiorly. Conjunctival injection was absent.

Two drops of retinoic acid were placed in the right eye and two drops of placebo in the left eye three times on the day of admission, and once daily thereafter. The next day (day two) the right (retinoic recipient) eye was clearly better: only minimal haze persisted centrally, the rest of the cornea being clear on hand-light examination. The area of corneal xerosis was gone and the stroma less edematous. In contrast, the left cornea retained its diffuse, moderate haze; xerotic patch; and stromal edema. Both eyes had developed minimal conjunctival injection, which was gone by day three.

Case 3—A 2-year-old normally nourished Indonesian boy had moderate corneal xerosis bilaterally, the right eye worse than the left. Retinoic acid was applied to the right eye and placebo to the left daily for the first three days and three times a day thereafter.

The first follow-up slit-lamp examination, on day three, revealed partial resolution in both eyes. Large numbers of brightly staining punctate lesions persisted inferiorly in both eyes, but many more on the left than on the right. By day four punctate keratopathy had all but disappeared from the right cornea, whereas large numbers of densely staining lesions persisted on the left.

Case 4—A 2-year-old severely malnourished (grade 3) Indonesian girl had diffuse moderate corneal haze, corneoscleral limbal xerosis for 360 degrees, and small, clear, central ulcers bilaterally (×3A). The ulcer in the right eye was approximately .50 corneal depth, whereas that on the left was only 0.33, and two heavy paracentral xerotic patches were present on the right cornea, but none on the left. Both corneas had marked, generalized stromal edema, their thickness three to four times normal. No infiltrate was present in either eye. Densely packed, brightly staining punctate epithelial lesions covered both corneas.

The right eye recieved two drops of retinoic acid and the left eye two drops of placebo three times a day for the duration of hospitalization. Both eyes received gentamicin and a combination bacitracin-neomycin-polymyxin ointment five times a day, always at least one hour after the most recent application of the retinoic acid or placebo.

By the next day (day two), the right (retinoic recipient) eye, which had originally been the more severely involved, was clearly better than the left. The ulcer was shallower (0.20 corneal depth) and surrounded by a thin rim of infiltrate, and the stromal edema had decreased significantly. In marked contrast, the left (placebo recipient) eye was worse than on admission. The stromal edema was unchanged or greater and the ulcer deeper. A thin rim of infiltrate had formed about the ulcer, however. Punctate keratopathy in the right eye was less dense and no longer involved the superior quadrant; it was unchanged in the left eye.

By day three both eyes showed improvement. By day eight the right cornea was entirely healed, with dense, vascularized scarring in the area of the original ulcer, whereas the left cornea still had diffuse moderate haze, stromal edema, and a fluorescein-positive, less densely scarred, and vascularized ulcer. Punctate keratopathy had disappeared on the right, but was still extensive on the left.

At no time did the conjunctival injection, present on admission, worsen. It was gone by the eighth hospital day.

DISCUSSION

Dietary supplementation with retinoic acid is an established means of prevent-

ing corneal destruction in vitamin A-deficient rats.[3] Pirie[4] theorized that corneal healing in xerophthalmic, malnourished children treated with systemic vitamin A might be delayed by the reduction in circulating retinol binding protein that commonly accompanies protein deficiency. She found that a single daily drop of 0.1% retinoic acid in arachis oil administered topically to vitamin A-deficient rats reduced the incidence of corneal perforation and degree of stromal edema. The only side effect was mild to moderate conjunctival injection.

Having observed a one-to-four day delay in corneal healing in many of our xerophthalmic patients, during which some suffered worsening of their lesions, we began a preliminary trial of topically applied 0.1% retinoic acid.

Only one of the eight children treated to date demonstrated any conjunctival injection, which was mild and equally apparent in the placebo-treated eye, and disappeared spontaneously the following day. Retinoic acid, 0.1% in arachis oil, appears to be safe when applied to intact globes of vitamin A-deficient children as frequently as three times a day.

Four of our eight patients, described here in detail, had symmetrical disease. Comparison of the retinoic acid and placebo-treated eyes suggests topical retinoic acid may be an effective means of initiating early corneal healing, before systemically administered vitamin A begins to have its effect. In every instance the retinoic acid-treated eye responded earlier and healed more quickly than its placebo counterpart. The difference was understandably more apparent in patients receiving more frequent administration of the retinoic acid.

Therapy with retinoic acid, however, is at best only adjunctive. Retinoic acid can only fulfill some of the functions of vitamin A, and few of these if applied topically. Every child with active xerophthalmia requires immediate, massive, systemic vitamin A therapy.

SUMMARY

Eight children with corneal xerophthalmia (×2 or ×3A) received standard high-protein diets and massive systemic vitamin A therapy. Retinoic acid, 0.1% in oil, was applied daily to one eye, and oil alone to the other. Topical retinoic acid proved safe and effective in speeding corneal healing, especially during the first critical days.

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ACYCLIC ANTIMETABOLITE THERAPY OF EXPERIMENTAL HERPES SIMPLEX KERATITIS

DEBORAH PAVAN-LANGSTON, M.D., ROBERT CAMPBELL, M.D., AND JONATHAN LASS, M.D.

Boston, Massachusetts

Although ocular antiviral drugs, vidarabine, idoxuridine and trifluorothymidine (F_3T), are highly effective against infectious herpes simplex keratitis, all may produce toxic side effects such as punctate keratopathy, cicatricial conjunctivitis and punctal occlusion.[1–4] Additionally, none has great potential as a systemic agent capable of eliminating viral neuronal reservoirs, which is the source of recurrent infection, caused by marked systemic toxicity, poor solubility, or rapid inactivation by the host. The basic mechanism for this toxicity is caused by the adverse effects these drugs have on host chromosomal structure, their being nonspecifically detrimental to normal host and viral DNA.[5–8]

Efforts to improve the selectivity of antiviral agents have resulted in the development and evaluation of the acyclic derivatives of purine nucleosides in which the side chains spatially mimic certain sugars. Acycloguanosine (9-[2-hydroxyethoxymethyl] guanine) stands out in preliminary studies as being effective against herpes simplex types 1 and 2 and varicella zoster virus. Acycloguanosine differs from the other antivirals in that it is activated specifically by viral-induced thymidine kinase, thereby sparing normal uninfected cells from disruption of nucleic acid synthesis.[9,10] Such specificity for viral infected cells results in a notable lack of host toxicity while allowing a "targeting-in" on those cells carrying the invading organism.

We report herein our findings from a masked, controlled study evaluating the therapeutic efficacy of unguent 3% acycloguanosine, 0.5% idoxuridine IDU (II), and 3% vidarabine on experiemntal ocular herpes simplex 1 infection in rabbits.

MATERIAL AND METHODS

Commercially available 0.5% idoxuridine and 3% vidarbine were used and compared to 3% acycloguanosine ointment, all in petrolatum base. Placebo controls received petrolatum base alone. All drugs were given five times daily for six days beginning four days after viral inoculation.

Acycloguanosine was synthesized and supplied in 3% ointment form. Pilot studies done by Burroughs Wellcome indicated that the minimal effective concentration for ocular herpes was 2% ointment, and that no toxicity occurred using concentrations up to 6%. Three percent ointment was selected for study to cover the range of susceptibility of the herpes simplex virus group to prevent the development of resistant strains by avoiding minimal effective dosing.

The unscarified eyes of 30 albino male rabbits were inoculated with McKrae strain type 1 herpes simplex virus SV ($TCID_{50}$ 10^{-9}), and the closed eyes were

From the Department of Cornea Research, Eye Research Institute of Retina Foundation, and the Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts. This study was supported in part by Research Grants EYNS-02268, EY-05206, and EY-05526, Program Project No. EY-00208, Institutional National Research Service Award EY-07018, Biomedical Research Support Grant PHS 5S07RR05527 from the National Eye Institute, National Institutes of Health; and in part by the Massachusetts Lions Eye Research Fund, Inc.

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Reprint requests to Deborah Pavan-Langston, M.D., Eye Research Institute of Retina Foundation, 20 Staniford St. Boston, MA 02114.

massaged gently for 30 seconds. By the fourth day post inoculation, all animals in the study had developed gross clinical disease. After equivalent grouping based on slit-lamp examination, the animals were divided into treatment groups.

All rabbit eyes were read daily on the slit lamp, scoring on a 0 to 4 basis of increasing severity of involvement. Corneal epithelial scores were as follows: 1^+ represented 25% surface ulceration, up to 4^+ represented 100% loss of cells. Stromal scores were as follows: 1^+ represented mild edema and haze, up to 4^+ represented severe edema with obscuring of anterior chamber details. Conjunctival scores related to degree of hyperemia were as follows: 1^+ represented mild injection, up to 4^+ represented severe congestion with edema.

Viral cultures were taken from all eyes at the beginning and end of the treatment periods, and inoculated immediately into primary rabbit kidney monolayer tissue culture.

Statistical analysis of data was done by a two-way analysis of variance, comparing treatment vs time at a 95% confidence level.

RESULTS

All control animals (11 eyes) developed disease during the first seven days after inoculation, and then improved spontaneously. While no animal in any antiviral treatment group developed curves, there was a notable difference in the three therapeutic response curves. The most striking and rapid improvement was in the acycloguanosine group (18 eyes), with improvement evident within 24 hours and continued improvement throughout the treatment period. Both idoxuridine (13 eyes) and vidarabine (13 eyes) showed similar improvement, but vidarabine worsened on days six and seven post inoculation before steadily improving, and idoxuridine worsened on days seven through nine post inoculation. Both drug groups had similar scores on the last day of therapy.

Mean curves of the corneal epithelial ulceration scores are shown in Figure 1, and the mean daily readings per treatment group are shown in Table 1.

Statistical analysis of these curves indicated that throughout the treatment period acycloguanosine was significantly better than controls, and on days eight and nine post inoculation, the other treatment groups at a 95% confidence level. Both vidarabine and idoxuridine were significantly better than controls at the same confidence level but idoxuridine was significantly better than vidarabine on days six and seven post inoculation, although not significantly better on days eight and nine post inoculation.

No significant stromal disease developed in any treatment group.

The mean curves obtained for iritis

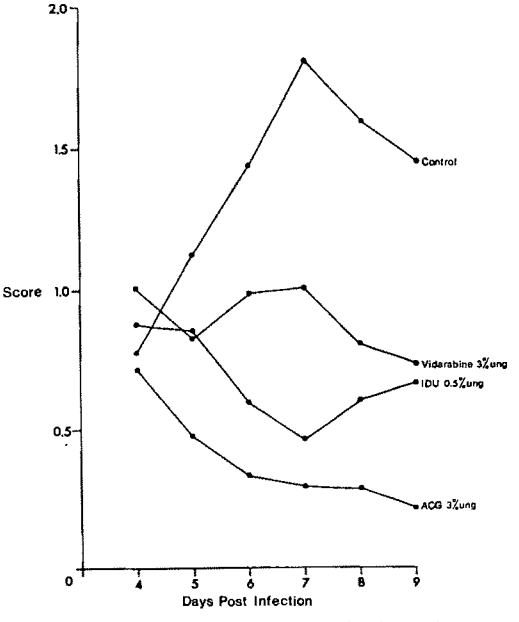


Fig. 1 (Pavan-Langston, Campbell, and Lass). Mean epithelial ulceration therapeutic response curves by treatment group.

TABLE 1

DAILY MEAN OF EPITHELIAL ULCERATION SCORES BY TREATMENT GROUP*

Treatment Group	Days Post Infection					
	4	5	6	7	8	9
ACG 3% ointment No. = 18	0.72	0.48	0.34	0.30	0.29	0.22
Vidarabine 3% ointment No. = 13	1.09	0.83	0.99	1.01	0.81	0.74
IDU 0.5% ointment No. = 13	0.77	0.84	0.62	0.53	0.61	0.60
Controls No. = 11	0.69	1.44	1.81	2.11	2.07	1.67

*ACG designates acycloguanosine; IDU, idoxuridine.

TABLE 2

DAILY MEAN SCORES OF IRITIS BY TREATMENT GROUP*

Treatment Group	Days Post Infection					
	4	5	6	7	8	9
ACG 3% ointment No. = 18	0.29	0.30	0.27	0.31	0.24	0.29
Vidarabine 3% ointment No. = 13	0.40	0.44	0.60	0.62	0.63	0.62
IDU 0.5% ointment No. = 13	0.35	0.42	0.25	0.41	0.41	0.41
Controls No. = 1	0.32	0.66	0.77	0.85	1.09	1.24

*ACG designates acycloguanosine; IDU, idoxuridine.

(Fig. 2, Table 2) and conjunctivitis (Fig. 3, Table 3) revealed a similar separation of curves with the results of all treatment groups being better than in the control groups and results of acycloguanosine being better than idoxuridine which, in turn, was somewhat better than vidarabine. There was no statistically significant difference between idoxuridine and vidarabine at 95% confidence level on day nine post inoculation, although acycloguanosine was better than vidarabine at a 95% confidence level. No toxic effects from any drugs were noted; that is, punctate keratopathy, increasing iritis, or conjunctivitis.

The results of viral cultures taken before and at the end of the treatment period were most interesting (Table 4). All eyes were positive before treatment. On treatment day six there was no statistically significant difference in the number of eyes positive among the controls, vidara-

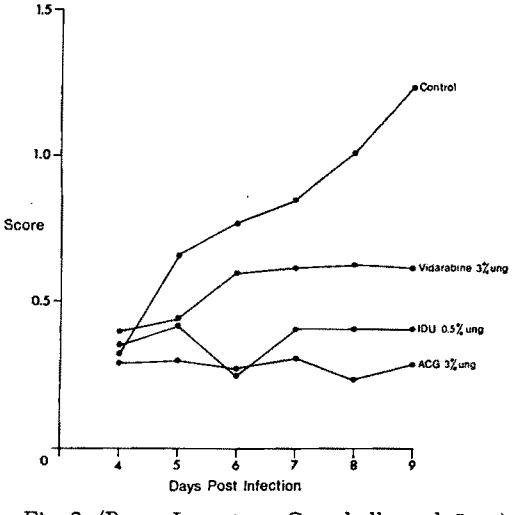


Fig. 2 (Pavan-Langston, Campbell, and Lass). Mean iritis therapeutic response curves by treatment group.

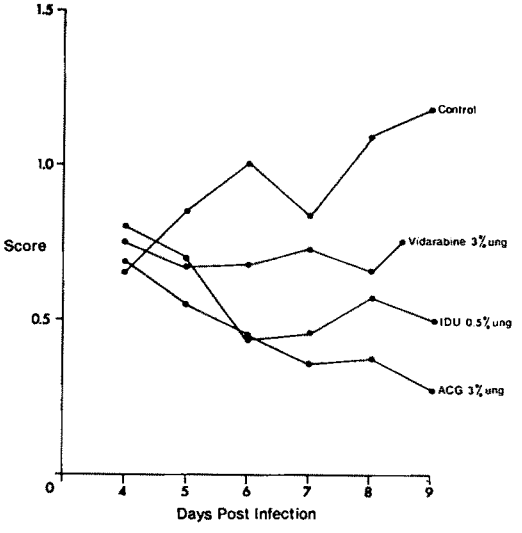


Fig. 3 (Pavan-Langston, Campbell, and Lass). Mean conjunctivitis therapeutic response curves by treatment group.

TABLE 3

DAILY MEAN SCORES OF CONJUNCTIVITIS BY TREATMENT GROUP*

Treatment Group	Days Post Infection 4	5	6	7	8	9
ACG 3% ointment No. = 18	0.69	0.55	0.45	0.36	0.38	0.28
Vidarabine 3% ointment, No. = 13	0.75	0.67	0.68	0.73	0.66	0.76
IDU 0.5% ointment No. = 13	0.80	0.70	0.44	0.46	0.58	0.50
Controls No. = 11	0.65	0.85	1.07	0.84	1.10	1.19

*ACG designates acycloguanosine; IDU, idoxuridine.

bine and idoxuridine groups; 100% for the first two (11/11, 13/13) and 93% for idoxuridine (12/13). Acycloguanosine, however, was strikingly lower with only 39% (7/18) of eyes positive for virus. This was significantly better than all groups at the 95% confidence level.

DISCUSSION

Acycloguanosine is a white, crystalline acyclic purine derivative with a solubility of 0.12% in water (Fig. 4). The mechanisms of action are not fully known at this time but those that are may be summarized as follows.[9,10] In vitro studies indicate that acycloguanosine enters herpes simplex virus infected cells to a much greater extent than normal cells. The drug is then converted to its monophosphate

TABLE 4

VIRAL CULTURES*

Drug	No. Eyes	Negative (%)	Positive No.† (%)	Negative
ACG	18	61	39	11
IDU	13	7.5	92.5	1
Vidarabine	13	0	100	0
Control	11	0	100	0
Total	50			

*ACG designates acycloguanosine; IDU, idoxuridine.

†All precultures were positive.

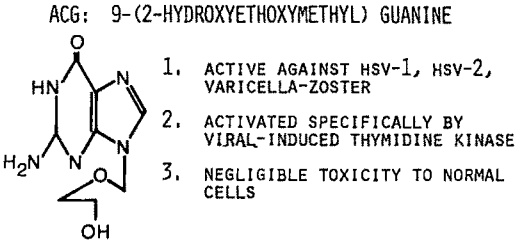


Fig. 4 (Pavan-Langston, Campbell, and Lass). Structure and therapeutically advantageous properties of acycloguanine; HSV designates herpes simplex virus.

form (acyclo-guanosine-monophosphate, guanine monophosphate) by specific viral-induced thymidine kinase, and from there to its bi- and triphosphates (acycloguanosine triphosphate) by enzymes yet to be determined. Acyclo-guanosine triphosphate acts by competitive inhibition against the incorporation of deoxyguanosine triphosphate into DNA via the DNA polymerase system (Fig. 5). The reduction of viral DNA polymerase activity is much greater than that of cellular DNA polymerase, which results in greater inhibition of viral DNA synthesis in comparison to normal cellular DNA synthesis. Preliminary data indicate that there is no significant conversion of acycloguanosine to its active triphosphate counterpart in uninfected cells, thereby markedly reducing the toxic potential of the drug.

The present study on the ocular therapeutic effectiveness of topical acycloguanosine in treating experimental herpes simplex virus keratitis indicates that this drug is significantly better than either of the current commercially available anti-

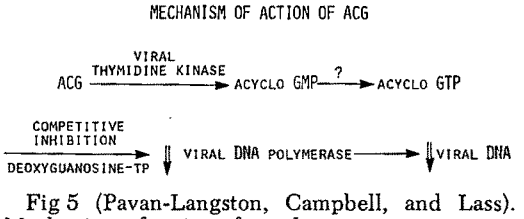


Fig 5 (Pavan-Langston, Campbell, and Lass). Mechanism of action of acycloguanine.

virals. The rapidity with which the acycloguanosine treated corneal ulcers healed, and the marked reduction in viral recovery from these eyes indicates both a high therapeutic efficacy and low toxicity. The difference between the vidarabine and idoxuridine curves has not previously been noted in our laboratory, in our own clinics, or in those of others; this may reflect our use of a higher titer of infecting virus ($TCID_{50}$ 10^{-9}) than that used in earlier studies.[1,3,11] The iritis and conjunctivitis scores reflect only the severity of the corneal disease, and certainly do not hint at the toxicity noted in previous studies with adenine arabinoside monophosphate.[12,13]

Acycloguanosine's activation only by virus-infected cells prevents the problems encountered with antimetabolites which are nonspecifically taken up and activated by infected and noninfected cells. In this respect, the drug is analogous to another new antiviral, 5-iodo-5′-amino 2′5′-dideoxyuridine (AIU),[14] which like acycloguanosine is metabolized, in vitro, only by herpes simplex virus-infected cells with the initial phosphorylation being mediated by herpes simplex virus-specific thymidine kinase. AIU triphosphate is then incorporated into both viral and cellular DNA within the infected host cell alone. In our laboratory, 10% AIU ointment used every six hours for 72 hours indicated that this drug is as effective as 0.5% idoxuridine ointment in experimental herpes simplex virus keratitis without any evidence of toxic side effect.[15] This might be expected, as at molar concentrations of AIU, vidarabine, idoxuridine and F_3T, which produced a comparable degree of inhibition of herpes simplex virus in vitro, only AIU was totally devoid of cellular toxicity (D. Ward, N. Ruddle, and W. Prusoff, unpublished data). Similarly, teratologic studies using AIU doses as high as 450 mg/kg/day in neonatal mice revealed no developmental defects, in marked contrast to idoxuridine, which was given in doses half as great (D. Albert, unpublished data).

Therapy of herpetic disease may be entering a new era. The approach with nonspecific, and therefore toxic, antimetabolites is being replaced by drugs synthesized specifically for activation only by virus-infected cells. The marked therapeutic effectiveness of acycloguanosine in our study coupled with planned systemic studies of this nontoxic drug in the future, indicate that scientists may have succeeded in separating the previously narrow therapeutic-toxicity ratio encountered in current forms of antiviral therapy.

Summary

In a masked controlled study we compared 3% acycloguanosine, 0.5% idoxuridine, and 3% vidarabine ointments in therapy of experimental herpes simplex virus keratitis in rabbits. The results of the acycloguanosine group were significantly better than the control groups and both other treatment groups, while producing none of the toxic side effects of increasing iritis, conjunctivitis or stromal keratitis, with continued drug application.

Acknowledgment

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UNPLANNED EXTRACAPSULAR CATARACT EXTRACTION IN POSTVITRECTOMY EYES

SANFORD M. MEYERS, M.D., RONALD KLEIN, M.D.,
SURESH CHANDRA, M.D., AND FRANK L. MYERS, M.D.
Madison, Wisconsin

Lens opacities may develop or progress after pars plana vitrectomy,[1,2] necessitating subsequent lens extraction. We describe herein the complication of unplanned extracapsular cataract extraction with loss of lens material into the vitreous cavity in three postvitrectomy patients.

SUBJECTS AND METHODS

Three patients developed cataracts after undergoing pars plana vitrectomy for vitreous hemorrhage. Cataract surgery in these patients resulted in unplanned extracapsular lens extractions.

CASE REPORTS

Case 1—A 70-year-old man with diabetes mellitus since age 30 years had proliferative diabetic retinopathy and recurrent vitreous hemorrhages in both eyes. The right eye underwent a pars plana vitrectomy in November 1974. Preoperatively, the right lens had 2+ nuclear sclerosis and 2+ posterior subcapsular lens changes. During the vitrectomy, the posterior lens capsule may have been touched with the instrument. Two months after vitrectomy a dense cataract was seen, and cataract surgery was done in the right eye. The surgical technique included massage of the globe after retrobulbar anesthesia and a conventional ab externo incision. After alpha chymotrypsin instillation, posterior displacement of the iris was noted. Cryoextraction resulted in lens rupture with loss of the lens nucleus into the posterior vitreous cavity. Most of the lens cortical material was removed with irrigation. The eye remained quiet for the next eight months. Then the lens nucleus dislocated into the anterior chamber, resulting in uveitis and secondary glaucoma. The first attempt to remove the lens nucleus from the anterior chamber failed because the lens nucleus dislocated back into the vitreous cavity. Five days later the lens nucleus again dislocated into the anterior chamber, and this time, 3% carbachol was used to achieve pupillary constriction, and the lens nucleus was removed with a lens loop through an inferotemporal limbal scleral incision with the patient sitting at a 45-degree angle. Postoperatively, the uveitis and secondary glaucoma decreased, but bullous keratopathy secondary to endothelial damage persisted. Intraocular pressure by applanation tonometry was 28 mm Hg in the right eye without medication. A Gunderson flap was done for comfort.

Case 2—A 59-year-old woman with diabetes mellitus for 15 years had a vitreous hemorrhage in the right eye for one year. In September 1977 an uncomplicated pars plana vitrectomy was done in the right eye. Preoperatively, there were 1+ posterior subcapsular lens opacities and 1+ to 2+ nuclear sclerosis in the right eye. During the next two months a dense cataract developed in the right eye. In November 1977, cataract surgery was done. Massage of the globe after retrobulbar anesthesia and a conventional ab externo incision were done. After alpha chymotrypsin instillation, the lens was loose. During cryoextraction, the capsule ruptured. All of the lens was removed with cryoextraction and irrigation except for three small pieces of lens cortex, which fell back into the vitreous cavity near the inferior retina. The lens cortical material in the vitreous cavity was absorbed without complication during the next two months.

Case 3—A 57-year-old hypertensive woman had a branch vein occlusion in the right eye in September 1973 and subsequently developed a vitreous hemorrhage in the right eye in May 1974. In January 1976 the patient had a pars plana vitrectomy in the right eye. Preoperatively, the right lens was clear. During the vitrectomy, the surgeon probably touched the lens with the instrument. In March 1976 a dense cataract was noted in the right eye, which had an intraocular pressure of 30 mm Hg as measured by applanation tonometry. Cataract extraction was performed on the right eye in March 1976. Massage of the globe after retrobulbar anesthesia and a conventional ab externo incision were performed. Enzyme was not used. During cryoextraction the lens ruptured, and irrigation was done. Most of the lens was extracted, but a significant amount of lens material was lost into the vitreous cavity. Postoperatively, there were cells and flare and a hyphema in the anterior chamber. A cyclitic membrane formed, the anterior chamber angle shallowed, and the intraocular pressure decreased as the right eye developed phthisis bulbi.

From the Department of Ophthalmology, University of Wisconsin, Madison, Wisconsin. This study was supported in part by Research Grant No. 5-T01-EY-00039 from the National Eye Institute.

Reprint requests to Sanford M. Meyers, M.D., Department of Ophthalmology, University of Colorado Medical Center, 4200 E. Ninth Ave., Denver, CO 80262.

Discussion

Cataract surgery in three postvitrectomy patients resulted in unplanned extracapsular extractions with loss of lens material into the vitreous cavity. The major etiologic factor in two of these cases was supposedly contact of the lens with damage to the posterior capsule during the previous pars plana vitrectomy. Other factors that may have contributed to this complication were: massage of the globe after retrobulbar anesthesia and use of alpha chymotrypsin during cataract surgery, and disruption of the anterior hyaloid face during the previous pars plana vitrectomy. Massage of the globe after retrobulbar anesthesia may cause posterior dislocation of lens material if the lens capsule has been injured during the previous vitrectomy. Similarly, enzyme zonulolysis may also precipitate posterior lens dislocation in vitrectomized eyes because of the disrupted anterior face and the low viscosity fluid in the vitreous cavity.

The consequences of an extracapsular cataract extraction in a postvitrectomy eye are potentially serious. A large amount of lens material, especially the nucleus, remaining in the vitreous cavity may induce uveitis, phacolytic glaucoma, or phacoanaphylaxis, as in Cases 1 and 3. Because of this, if lens injury occurs during vitrectomy and produces central posterior lens changes, one must consider immediate lens extraction because of the high probability of a subsequent cataract.[3] However, the feathery posterior lens changes, which may develop during long vitrectomies, are frequently reversible in young patients, and one need not remove these lenses unless visualization during surgery is impaired.

In postvitrectomy eyes, both the patient and surgeon should be aware that cataract surgery can be more hazardous than usual. The following measures may be helpful in minimizing the risk of an unplanned extracapsular extraction in these eyes when using a conventional ab externo cataract technique and cryoextraction: either avoid massage of the globe after retrobulbar anesthesia or use only gentle massage, use Flieringa's ring to prevent collapse of the eye, allow a larger than usual iceball to form with the cryoprobe, use a lens spoon or loop to support the lens during cryoextraction, avoid excessive manipulation of the lens,[4] and avoid the use of alpha chymotrypsin[4] or immediately apply the cryoprobe to the lens after enzyme instillation.

With a soft cataract, one may use a vitrectomy instrument via the pars plana for the lens extraction. With this approach, the surgeon can easily remove lens material from the posterior vitreous cavity if the need arises. Some surgeons may also consider a planned extracapsular cataract extraction in postvitrectomy eyes, especially in younger patients, to be more certain of removing the nucleus.

If an unplanned extracapsular cataract extraction occurs in a vitrectomized eye, indirect ophthalmoscopy can be used to determine if any lens fragments are present in the posterior vitreous cavity. A few small pieces of lens material, especially cortical fragments, usually will absorb spontaneously without difficulty,[3–5] as in Case 2. However, a substantial amount of residual lens material, especially the nucleus, needs to be removed because a marked inflammatory response often occurs, as in Cases 1 and 3. To remove the residual lens material, irrigation and gentle aspiration through the cataract incision can be attempted. However, if this is unsuccessful, one may consider an immediate or subsequent pars plana vitrectomy if needed.

Summary

A 70-year-old man, a 59-year-old woman, and a 57-year-old woman underwent pars plana vitrectomy. In all three cases,

cataracts developed in the eyes that had been operated on. During cataract extraction, which included massage of the globe after retrobulbar anesthesia and a conventional ab externo incision, loss of lens material into the vitreous cavity occurred in all three postvitrectomy eyes.

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OPHTHALMIC MINIATURE

"You may hear, therefore as it is all past I may tell you that on the 10th of July last a shot having struck our battery the splinters of stone from it struck me most severely on the face and breast. Although the blow was so severe as to occasion a great flow of blood from my head, yet I most fortunately escaped by only having my right eye nearly deprived of its sight. It was cut down, but is as far recovered as to be able to distinguish light from darkness, but as to all the purpose of use it is gone. However, the blemish is nothing, not to be perceived unless told. The pupil is nearly the size of the blue part, I don't know the name."

Nelson's Letters To His Wife and Other Documents, 1785-1831
Edited by-George P. B. Naish
London, Navy Records Society, 1958

CONGENITAL VARICELLA CATARACT

EDWARD COTLIER, M.D.
New Haven, Connecticut

Maternal varicella was first recognized as a cause of congenital anomalies by Laforet and Lynch[1] who described a "poorly developed infant with cortical atrophy, cicatricial skin lesion over the left lower extremity, undescended testicles, defective development of the toes of the right foot and bilateral optic atrophy with a peculiar darkish pigmentation of the retina." There was bilateral nystagmus and the pupils showed "only questionable reaction to light."

McKendry and Bailey,[2] and Charles, Bennett, and Margolis[3] documented chorioretinitis by ophthalmoscopy, in infants with congenital varicella. Histopathologic evidence of lens involvement was noted in their cases of two infants and in the case of Srabstein and associates.[4] We report herein a case of unilateral congenital cataract secondary to maternal varicella in a 16-month-old infant who underwent successful cataract surgery. Persistent antibody titers to varicella zoster virus were present, but virus was not recovered from the lens aspirates. Congenital cataracts secondary to maternal herpes zoster have been previously described.[5] Additionally, Srabstein and associates[6] briefly mentioned bilateral cataracts and microphthalmos in a girl who died at 6.5 months of age from complications secondary to congenital varicella.

From the Department of Ophthalmology and Visual Science, Yale University School of Medicine, New Haven, Connecticut. This study was supported by National Institutes of Health grants EY-00785 and EY-02490.

Reprint requests to Edward Cotlier, M.D., Department of Ophthalmology and Visual Science, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06510.

CASE REPORT

The infant was a normally developed and well-nourished 16-month old boy. The mother noticed a "white opacity in the left eye" one week after birth. He weighed 2,468 g at birth. In the fourth month of her pregnancy, the mother had been exposed to a child with varicella, and within two weeks, she had a varicelliform rash. Otherwise the pregnancy and delivery had been uncomplicated. She had taken no medications except vitamins as prescribed by the obstetrician. Psychomotor development of the child was within normal limits for his age. Dermatologic, orthopedic, and pediatric examination failed to detect any abnormalities except that the head circumference was in the tenth percentile. Chest x-rays were normal. Laboratory tests including urinalysis, complete blood cell count, protein electrophoresis, serum immunoglobulins A,G, and M, and calcium phosphorus in serum were normal. Serology for rubella, herpes simplex, toxoplasmosis, and cytomegalovirus were negative. Varicella zoster fluorescent antibody to membrane antigen titer was 1:16 on one occasion and 1:8 in a repeat test. Attempts to culture varicella zoster virus from throat swabs or urine were unsuccessful. Karyotype by Giemsa banding of chromosome revealed no abnormalities (46XY).

Ocular examination revealed fixation and following of the light only with the right eye. There was pupillary response to light in the left eye. Fifteen degrees of left estropia were measured by the corneal light reflex. The left eye was smaller than the right eye and had a mature cataract. After instillation of atropine 1% to both eyes, the pupil dilated to 8 mm in the right eye and to 7 mm in the left eye. Ultrasonography revealed slight shortening of the anteroposterior measurement of the left eye, but no evidence of retinal detachment or vitreous degeneration.

An extracapsular cataract extraction was performed in the left eye by means of mechanical suction, and the lens aspirate was plated for virus cultures. Neither varicella zoster nor rubella virus was recovered from the lens aspirate even after three passages. The postoperative period was uncomplicated, and ophthalmoscopy revealed no evidence of chorioretinal abnormalities. Refraction was R.E.: +0.25; L.E.: +6.50 sphere +0.50 at 90 1/4.

Maternal varicella zoster fluorescent antibody to membrane antigen titers were 1:8 in two successive blood testings.

DISCUSSION

The disappearance of rubella virus as a teratogenic and cataractogenic agent and

new precise virologic and serologic methods for determination of other viruses have revealed that varicella zoster virus causes some congenital malformations.[1-7] The present case represents an example of the cataractogenic potential of the varicella zoster virus.

Although vesicle fluid is infectious, the route for varicella zoster virus transmission among humans is not certain.[8] Nonimmune subjects can contract varicella (chickenpox) from patients suffering from herpes zoster. Virus shedding from varicella throat lesions may be transmitted by inhalation. However, herpes zoster lesions usually do not affect the mouth and the nose, and direct contact is necessary for spreading. The varicella zoster virus can be cultured only from fluid-containing lesions.[8] Dry skin lesions give negative cultures for varicella zoster virus. In contrast, smallpox scabs may harbor live virus for months.[8] Thus, virus has not yet been recovered from congenital varicella patients.[1-6] Maternal antibody varicella zoster virus, passively transferred, does not persist after 8 months of age; thus, titers of 1:8 to 1:32 are found only in convalescent children.[9]

A wide spectrum of lesions is present in congenital varicella, ranging from early death,[1,4] leukemia,[10] central nervous system involvement with cerebral or cerebellar atrophy,[1-3] and multiple congenital anomalies with rudimentary limbs and digits[1,2,6] to minimal involvement of the eye as in our case. The number and extent of lesions in congenital varicella may depend on the time of gestation at which the infection occurs. In the mothers of patients reported by McKendry and Bailey,[2] LaForet and Lynch,[1] Savage, Moosa, and Gordon,[6] and Dessermond and associates[7] varicella infection occurred during the 11th, eighth, ninth, and third week of pregnancy, respectively. Those children had gross malformations of the central and peripheral nervous system, skin, or limbs. Conversely, isolated involvement of the eye resulted from maternal infection during the fourth month of gestation in the patient of Charles, Bennett, and Margolis[3] and in our patient. Only one child in whom maternal varicella infection supposedly occurred between the 13th and 15th week of pregnancy had multiple neurologic and skin abnormalities in addition to cataracts and chorioretinopathy.[4]

The lens is susceptible to viruses. During the early stages of development, the lens epithelium actively synthesizes proteins. In experimental animals, cataracts and lens infections are inducible by the mumps virus,[11] St. Louis encephalitis virus,[12] SMCA virus,[13] Newcastle disease virus,[14] and rubella virus.[15] In humans, cataracts occur secondary to maternal transmission of rubella,[16] herpes simplex,[17] herpes zoster,[5] and cytomegalovirus.[18]

To my knowledge, ours is the first case of clinically documented congenital varicella cataract in a patient who underwent successful cataract surgery. Previously, Robb[19] reported cataracts secondary to varicella infection in a 3-year-old boy in whom cataract developed within six days after a generalized vesicular eruption had begun. In that case, varicella was not caused by maternal transmission during pregnancy. Varicella zoster serum titers should then be included in the diagnostic examination for congenital cataracts. The varicella zoster titers in our patient indicated that infection could have only taken place in utero. [9]

SUMMARY

A 16-month-old boy with 1:16 and 1:8 serum titers to varicella zoster fluorescent membrane antigen had had unilateral cataract and microphthalmos since birth. The mother had suffered varicella during

the fourth month of pregnancy. Cataract aspiration in the child was uncomplicated.

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MASSIVE SPONTANEOUS SUBRETINAL HEMORRHAGE

MICHAEL A. BLOOME, M.D., AND RICHARD S. RUIZ, M.D.
Houston, Texas

Massive spontaneous subretinal hemorrhage describes the sudden appearance of a massive retinal or choroidal hemorrhage, or both. The initial location of this hemorrhage has been described as either choroidal (massive, spontaneous choroidal hemorrhage)[1–5] or beneath the pigment epithelium (an extensive form of hemorrhagic detachment of the pigment epithelium)[6–8]; but, the blood may quickly extend into the neurosensory retina and vitreous. Regardless of the initial location of the hemorrhage, the importance of recognizing this entity is demonstrated by the numerous eyes that have been enucleated with a diagnosis of malignant melanoma.[9,10]

This hemorrhage appears as an elevated mass under the retina. It is usually greater than one quadrant in size and may involve the entire retina. The mass characteristically has smooth borders and varies from dark brown to bluish black in color. It frequently enlarges rapidly and the subsequent appearance of blood in and under the neurosensory retina (especially at the borders of the mass) is important in differentiating this lesion from a melanoma. Massive vitreous hemorrhage, either initially or later, is common and may make the diagnosis difficult. Because of its large size, the mass may displace the lens-iris diaphragm anteriorly, resulting in intractable angle-closure glaucoma.[5] In time the lesion develops into an elevated area of fibrosis surrounded by atrophy and proliferation of the pigment epithelium.

We describe herein eight patients with massive, spontaneous subretinal hemorrhage seen during the last 15 years.

CASE REPORTS

Case 1—A 58-year-old woman first seen in September 1965 had a history of blurred vision in the left eye of three weeks' duration. At this time, visual acuity was R.E.: 6/6 (20/20), and L.E.: finger counting. A vitreous hemorrhage was present in the left eye. Although the posterior pole could not be visualized because of the vitreous blood, a gray, elevated mass could be seen in the superior-nasal quadrant (Fig. 1). Examination of the right eye was normal. A radioactive phosphorus uptake (^{32}P) test comparing the superior-nasal quadrant of the left eye with the other three quadrants was negative. The mass did not transilluminate.

The patient was observed for 18 months with no treatment. By October 1966, the vitreous blood had completely cleared and the visual acuity was 6/6 (20/20). A large, elevated fibrotic scar surrounded by pigment proliferation was present in the superior-nasal quadrant (Fig. 2). The patient has subsequently been observed yearly with no change in the ocular examination.

Case 2—A 48-year-old woman first seen in December 1966 had a history of decreased vision in the right eye for one week. Visual acuity was R.E.: finger counting; L.E.: 6/4.5 (20/15). On the right, there was a large, dark, highly elevated mass under



Fig. 1 (Bloome and Ruiz). Case 1. Left eye, a dark elevated mass superior-nasally and extensive vitreous hemorrhage were present.

From the Department of Ophthalmology, University of Texas Medical School, Houston, Texas.

Reprint requests to Michael A. Bloome, M.D., Houston Eye Associates, 1100 Hermann Professional Building, Houston, TX 77030.



Fig. 2 (Bloome and Ruiz). Case 1. Left eye, one year later. A large, elevated scar surrounded by atrophy and proliferation of the pigment epithelium had replaced the elevated mass. Visual acuity was 6/6 (20/20).

the retina which covered the entire lower half of the fundus. A small mass surrounded by a thin layer of blood under the neuroepithelium was present in the macula (Fig. 3). The vitreous was clear, and the uninvolved left eye was normal.

The patient was hospitalized, and a ^{32}P test using the superior quadrants of the involved eye as controls was negative. One day later, a marked vitreous hemorrhage obscured further visualization of the fundus. During the subsequent year the hemorrhage organized into a dense membrane, and in September 1967, the right eye was enucleated because of the possibility of an occult neoplasm. Microscopic examination showed diffuse chorioretinal scarring consistent with a disciform type of degeneration and no evidence of a neoplasm or subretinal neovascularization.

Case 3—A 61-year-old man had a sudden onset of visual loss in the right eye in September 1967. He had previously had an ocular examination in 1963, at which time visual acuity in the right eye was 6/30 (20/100) and disciform degeneration of the macula was noted. The vision in the left eye, at that time, was 6/6 (20/20), but macular drusen were present. He had been taking numerous medications for hypertension, and in 1964 had been given anticoagulants for a myocardial infarction.

Visual acuity was light perception in the right eye and 6/7.5 (20/25) in the left eye. The right eye had a shallow anterior chamber and a pressure of 29 mm Hg, whereas the left eye was normotensive with a deep chamber. A solid, dark, elevated mass involved the entire right fundus. A large amount of blood was also present under the neuroepithelium and in the vitreous (Fig. 4). In the left eye, the previously noted macular drusen were present as well as three small subretinal hemorrhages nasal to the disk.

The patient was immediately hospitalized, and the anticoagulants were discontinued, with a rapid normalization of his clotting time. Despite this, the

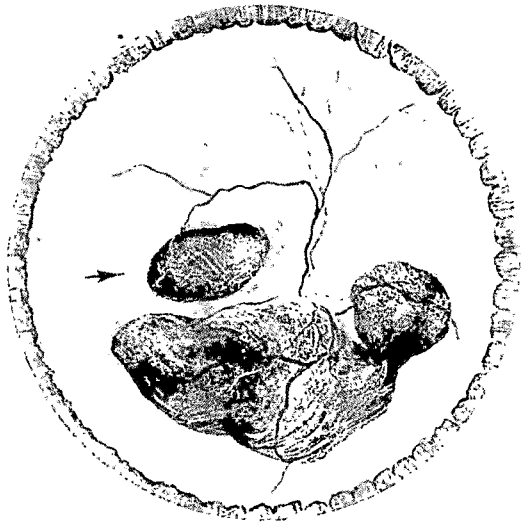


Fig. 3 (Bloome and Ruiz). Case 2. Right eye, a dark, elevated subretinal mass involved the lower retina. A smaller lesion surrounded by a thin layer of blood under the neuroepithelium (arrow) was present in the macula.

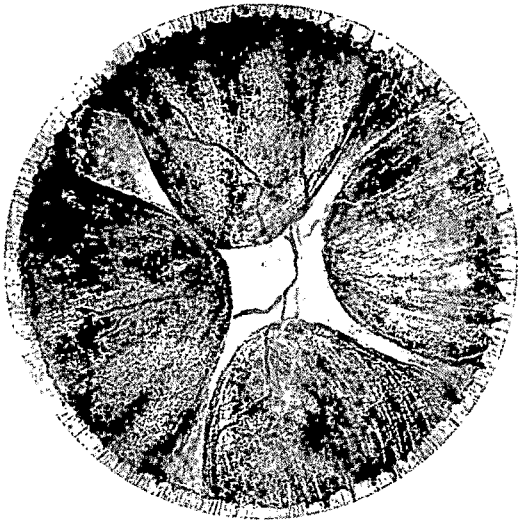


Fig. 4 (Bloome and Ruiz). Case 3. Right eye, a solid, dark elevated mass involved the entire retina. A large amount of blood was also present in the vitreous and under the neuroepithelium.

mass continued to increase in size during the next week, resulting in further forward displacement of the lens-iris diaphragm and an increase in the intraocular pressure. A ^{32}P test was attempted and interpreted as normal. Ten days after admission, the eye was enucleated because of intractable glaucoma and the absence of light perception.

Microscopic examination revealed a total hemorrhagic detachment of the retina as well as marked hemorrhage under the pigment epithelium and in the choroid and suprachoroidal space (Fig. 5). No subretinal neovascularization could be seen, although the massive amount of hemorrhage made the microscopic examination difficult.

The patient had an uneventful recovery and maintained good vision in the left eye until April 1970, at which time a retinal tear accompanied by vitreous hemorrhage resulted in a sudden decrease in vision. The patient died of a myocardial infarction in November 1972.

Case 4—A 47-year-old woman first seen in February 1968 had a history of blurred vision and floaters in the left eye for two days. She had been in excellent health, although there was a family history of diabetes mellitus.

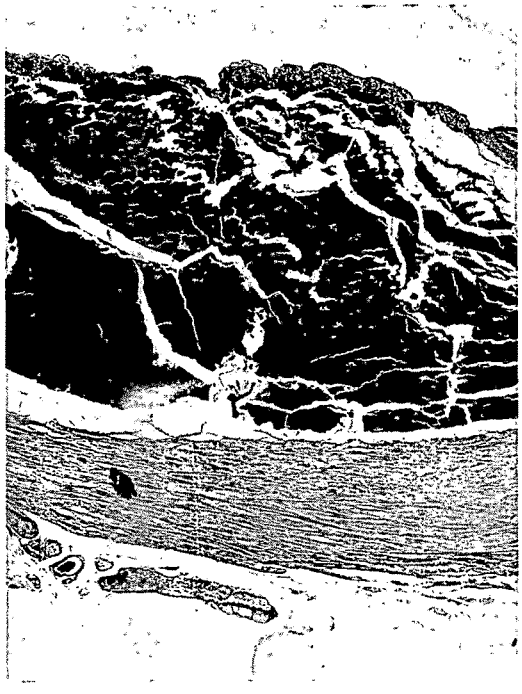


Fig. 5 (Bloome and Ruiz). Case 3. Histologic section of enucleated eye. Marked hemorrhage was present in both the choroid and suprachoroidal space. The retina and pigment epithelium were also detached by the hemorrhage and are not present in this field (hematoxylin-eosin, × 45).

Visual acuity was hand motion temporally in the left eye and 6/7.5 (20/25) in the right eye. A marked vitreous hemorrhage was present in the left eye; but, with an indirect ophthalmoscope, a solid dark mass could be seen temporally and inferiorly. A moderate amount of blood under the neuroepithelium surrounded the mass (Fig. 6). Examination of the right eye was normal.

The patient was hospitalized, and a ^{32}P test using the superior-nasal quadrant as a control was negative. She was subsequently observed with no treatment. The vitreous hemorrhage slowly resolved and, in June 1971, the visual acuity of the left eye was hand motions. A diffuse posterior subcapsular cataract was noted on slit-lamp examination. Two large, elevated scars were present in the inferotemporal and nasal quadrants and were surrounded by atrophy and proliferation of the pigment epithelium (Fig. 7). The right eye has remained normal.

Case 5—A 39-year-old woman first seen in February 1970 had a history of decreased vision in the left eye for several weeks. Visual acuity in this eye was 6/12 (20/40). A small subretinal hematoma was present superior to the macula, and two small atrophic areas were situated between the macula and disk. Visual acuity in the uninvolved eye was 6/6 (20/20), and the ocular examination was normal. The patient was treated with systemic corticosteroids for one month, during which time her visual acuity improved to 6/6 (20/20) and was accompanied by a slight decrease in the size of the lesion. In April 1970, the visual acuity suddenly decreased to 6/60 (20/200) with an enlargement of the lesion and extension into the macula (Fig. 8). During the next



Fig. 6 (Bloome and Ruiz). Case 4. Left eye, a dark, elevated mass occupied the entire temporal and inferior retina. Marked vitreous hemorrhage was also present.

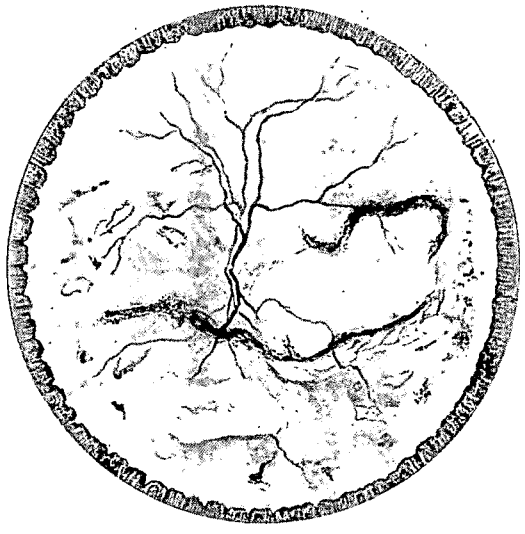


Fig. 7 (Bloome and Ruiz). Case 4. Left eye, three years later. Two elevated scars surrounded by atrophy and proliferation of the pigment epithelium had replaced the subretinal hemorrhage.

month, a massive vitreous hemorrhage reduced the visual acuity to light perception and totally obscured fundus visualization.

The patient was lost to follow-up for five years, during which time a similar episode occurred in the right eye. In April 1975, she was again examined. The visual acuity was light perception in the right eye and hand motions in the left eye. A mature cataract was present in the right eye, and the fundus could not be seen. Although a diffuse posterior subcapsular cataract was present in the left eye, the fundus could be seen with an indirect ophthalmoscope. A large, fibrotic scar was present in the temporal retina, and a small scar was seen in the superior-nasal quadrant. Atrophy and pigment proliferation surrounded both lesions (Fig. 9).

Case 6—A 67-year-old man first seen in May 1971, had a history of decreased vision in the right eye for three days. He had also noticed a gradual decrease in vision in the left eye for several years. He had been taking antihypertensive medications and had been given anticoagulants three months previously for a myocardial infarction.

Visual acuity was hand motions in the right eye and 6/18 (20/60) in the left eye. On the right, a solid, dark, elevated mass involved the entire fundus except for a small central area. Although no vitreous hemorrhage was present, blood under the neuroepithelium surrounded the mass (Fig. 10). In the left eye, an old disciform scar was present in the temporal paramacular area.

The patient was subsequently observed by another ophthalmologist until May 1975, when we reexamined him. Visual acuity was light perception in the right eye and 6/18 (20/60) in the left eye. A mature cataract in the right eye prevented fundus visualization. The left eye was unchanged. Despite a

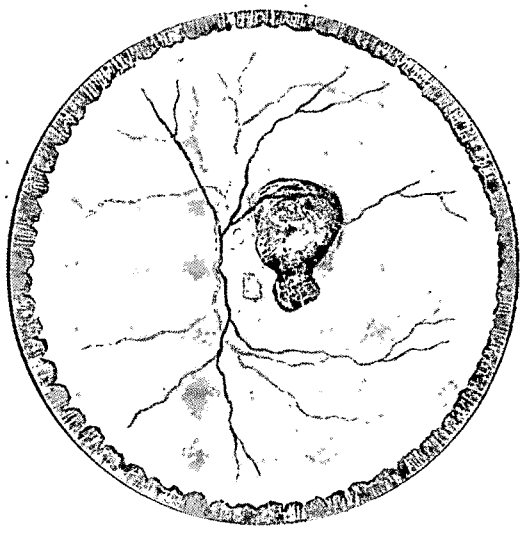


Fig. 8 (Bloome and Ruiz). Case 5. Left eye, the subretinal hematoma had extended into the macula reducing the vision to 6/60 (20/200). Two small atrophic scars were present between the disk and macula.

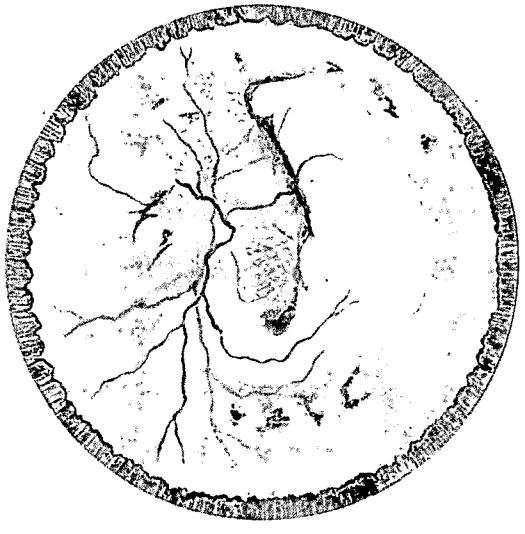


Fig. 9 (Bloome and Ruiz). Case 5. Left eye, five years later. A large, elevated scar surrounded by pigment proliferation was present in the temporal retina. Numerous areas of atrophy and pigment proliferation were scattered throughout the retina.

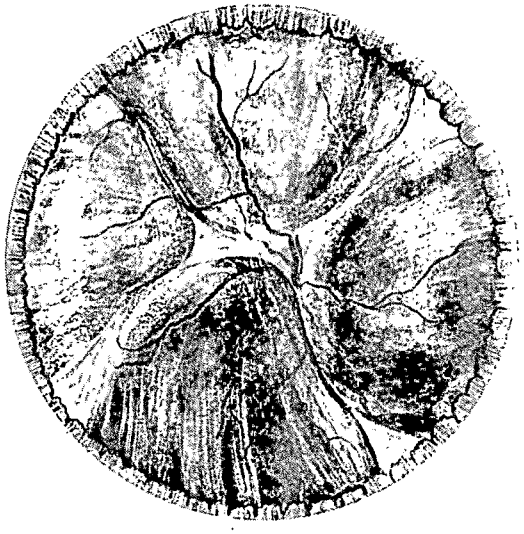


Fig. 10 (Bloome and Ruiz). Case 6. Right eye, a dark, elevated subretinal hematoma involved the entire retina.

guarded prognosis, the patient underwent an uneventful cataract extraction in June 1975. The best corrected visual acuity in the right eye following surgery was hand motions. Multiple areas of elevated fibrous tissue surrounded by pigment proliferation and atrophy were present in the retina (Fig. 11).

Case 7—A 43-year-old woman first seen in September 1972 had a history of decreased vision in the left eye for four days. Visual acuity was 6/6 (20/20) in the right eye and finger counting in the left eye. A large, dark elevated mass was present in the posterior pole of the left eye. Surrounding this lesion was an area of preretinal hemorrhage as well as a small hemorrhagic detachment of the pigment epithelium temporal to the lesion. The right eye was normal.

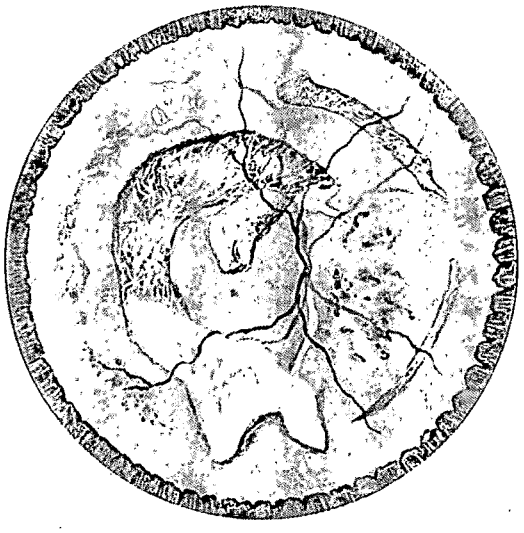


Fig. 11 (Bloome and Ruiz). Case 6. Right eye, five years later. The eye had recently undergone an uneventful cataract extraction. An elevated, crescentic scar surrounded by atrophy and pigment proliferation had replaced the subretinal hemorrhage.

Within a week after the initial examination, a massive vitreous hemorrhage obscured further visualization of the retina. The patient was observed for the next six months, during which time the vitreous blood resolved. In March 1973, visual acuity in this eye was 6/60 (20/200) and an elevated scar was seen superior to the macula. The patient was lost to follow-up.

Case 8—A 77-year-old man first seen in December 1974 had a history of decreased vision in the right eye for three weeks. He had been taking quinidine for atrial fibrillation as well as various antihypertensive medications. Visual acuity was finger counting in the right eye and 6/60 (20/20) in the left eye. On the right, a large, elevated dark mass was present in the macular area. The lesion was approximately five disk diameters in size and was surrounded by a ring of blood under the neuroepithelium. The left eye was normal except for a few macular drusen. A diagnosis of hemorrhagic detachment of the pigment epithelium secondary to disciform degeneration was made and the patient was observed. In February 1975, the visual acuity had improved to 6/60 (20/200), and a typical disciform scar was seen in the macula. Fluorescein angiography revealed a small area of subretinal neovascularization temporal to the scar. In July 1975, the vision in the involved right eye suddenly decreased to hand motions. Another larger, elevated mass now occupied the superior and inferior temporal quadrants, and its nasal border was adjacent to the previous scar. A moderate amount of vitreous blood was present. During the next six months, the vitreous blood cleared and the mass was replaced by a large, fibrotic scar surrounded by atrophy and proliferation of the pigment epithelium. The final visual acuity remained hand motion.

DISCUSSION

Although the number of patients in this series is relatively small, it is, to our knowledge, the largest series of massive spontaneous subretinal hemorrhage ever reported (Table).

The eight patients ranged in age from 39 to 77 years with only two patients under the age of 45 years. Four of our patients had a previous history of hypertension and two were taking anticoagulants at the time of their hemorrhage. Two patients had disciform macular degenera-

TABLE

SUMMARY OF CASE REPORTS*

Patient No.	Age, Sex (yrs)	Medical History	Initial Visual Acuity	Mass Size (Quadrants)	Vitreous Hemorrhage	^{32}P Test	Final Visual Acuity	Remarks
1	58,F	—	C.F.	1	+	—	6/6 (20/20)	
2	48,F	H	C.F.	2	+	—	E	
3	61,M	H,A	L.P.	4	+	—	E	S.D.D., Involved eye
4	47,F	—	H.M.	3	+	—	H.M.	
5	39,F	—	6/12 (20/40)	1	+	N.D.	H.M.	
6	67,M	H,A	H.M.	4	−	N.D.	H.M.	S.D.D., Other eye
7	43,F	—	C.F.	1	+	N.D.	6/60 (20/200)	
8	77,M	H	H.M.	2	+	N.D.	H.M.	S.D.D., Involved eye

*H signifies hypertension; A, anticoagulants; N.D., not done; E, enucleated; S.D.D., senile disciform degeneration; C.F., finger counting; H.M., hand motions; L.P., light perception.

tion in the involved eye before the hemorrhage and one other patient had a similar diagnosis in the uninvolved eye. The initial visual acuity varied from 6/12 (20/40) in one case to finger counting or less in seven cases and was dependent on the site and extent of the hemorrhage as well as the presence of vitreous blood. The final visual acuity was equally poor with one exception (6/6 [20/20]) and depended on the location of the scar tissue. The subretinal hemorrhages were large (two quadrants or more in six cases) and involved the entire fundus in two cases. Vitreous hemorrhage was present in seven cases and took from four months to three years to clear. In four cases, a ^{32}P uptake test was done, and all were negative. One patient developed angle-closure glaucoma caused by rapid enlargement of the mass with anterior displacement of the lens-iris diaphragm.

The blood in massive, spontaneous subretinal hemorrhage may originate either in the choroid or beneath the pigment epithelium. Older reports frequently described the hemorrhage as choroidal but the histologic descriptions were often vague and incomplete.[1–3] Similar cases have also been described as originating under the pigment epithelium but most of these cases were not documented histologically.[7,8] Regardless of the initial location of the hemorrhage, the clinical picture is frequently similar. Massive hemorrhage in the choroid or under the pigment epithelium, or both, results in a large, dark mass, and further extravasation of the blood anteriorly may result in blood under the retinal neuroepithelium (especially at the borders of the mass) and in the vitreous.

The clinical picture of massive, spontaneous subretinal hemorrhage can be caused by several entities. In cases resulting from hemorrhage under the pigment epithelium, the hemorrhage usually originates from a subretinal neovascular membrane which begins in the choriocapillaris and extends under the pigment epithelium after passing through or around Bruch's membrane.[11] This subretinal neovascularization has been described in numerous disorders, including macular and peripheral disciform degeneration, ocular histoplasmosis, macular drusen, and angioid streaks, and the like.[11–14] Most hemorrhages under the

pigment epithelium are typically much smaller and less extensive than those in our cases, but massive hemorrhages can occur. Cases 5 and 8 initially had typical hematomas under the pigment epithelium before developing massive hemorrhages. These cases, as well as a few described by Silva and Brockhurst,[7] probably represent an extensive form of hemorrhagic detachment of the pigment epithelium.

Some cases of massive, spontaneous subretinal hemorrhage (especially those with large masses involving the entire retina) originate in the choroid. Sien[4] described a case of spontaneous choroidal hemorrhage in which a ruptured posterior ciliary artery was demonstrated histologically. A similar mechanism has been demonstrated in expulsive choroidal hemorrhage during or following cataract extraction,[15-16] and also in a rare entity known as spontaneous expulsive choroidal hemorrhage, in which an expulsive choroidal hemorrhage follows corneal perforation in eyes with long-standing glaucoma.[17,18] Although these last two disorders differ from our cases in which no glaucoma or ocular hypotony was present, it is possible that a choroidal vessel weakened by arteriosclerosis may bleed spontaneously or during anticoagulant therapy. Choroidal hemorrhage may also originate from a subretinal neovascular membrane in the choriocapillaris before it penetrates Bruch's membrane.

Two of our patients with a previous history of disciform degeneration of the macula were taking anticoagulants before their hemorrhage. Wolter and McWilliams[19] and Feeman and associates[20] have reported cases of massive subretinal hemorrhage in patients with disciform macular degeneration who were given anticoagulants. Pouliquen and Rousselie[21] also reported a similar case in a patient with no previous ocular disorders. The massive hemorrhages seen in our two patients may have resulted from the use of anticoagulants. All ophthalmologists should be aware of this complication in patients with disciform degeneration of the macula.

Regardless of the anatomic origin or cause of the hemorrhage, the clinical picture must be recognized for proper management. A thorough history for the presence of hypertension, arteriosclerosis, and drugs such as anticoagulants is mandatory. A history of previous visual loss from macular disease or the finding of macular pathology in the other eye may also suggest the correct diagnosis.

Frequent fundus examinations with indirect ophthalmoscopy and scleral depression are the best means of confirming the diagnosis. The presence of a rapidly expanding mass is much more suggestive of subretinal hemorrhage than a tumor. The initial or subsequent appearance of blood under the retinal neuroepithelium and in the vitreous also points to a subretinal hemorrhage. The eventual appearance of an elevated area of fibrosis surrounded by atrophy and pigment proliferation establishes the diagnosis.

Unfortunately, the frequent presence of massive vitreous hemorrhage may obscure the fundus initially or prevent adequate follow-up examinations. If a patient has a vitreous hemorrhage (or if it occurs at a later date), bedrest with bilateral patches and head positioning may be helpful to facilitate viewing the lesion. Ultrasonography is essential when the retina cannot be visualized and is also helpful in following the mass when a late hemorrhage occurs.[22] A ^{32}P test is indicated if the lesion is suggestive of a melanoma and can be adequately localized with diathermy on bare sclera. A negative ^{32}P test makes the diagnosis of melanoma unlikely and warrants following the lesion closely. Ultrasonography is also useful in confirming the lesion's location before the ^{32}P test.

Once the diagnosis is confirmed, treatment should be conservative in hopes of

obtaining useful vision. If angle-closure glaucoma is present, drainage of the choroidal hemorrhage through a posterior sclerotomy and puncture of the choroid, as well as reformation of the anterior chamber, may be necessary.[5] A vitrectomy late in the course of the disease to remove old, organized blood may result in some visual improvement. A vitrectomy early in the disease may allow the fundus to be visualized but is a dangerous undertaking if an elevated mass is present.

SUMMARY

We studied eight cases of massive, spontaneous subretinal hemorrhage which was characterized by the sudden appearance of one or more large, dark, elevated hematomas under the retina. The initial location of the hemorrhage may have been in the choroid or under the pigment epithelium, or both, but further extravasation of the blood anteriorly frequently resulted in hemorrhage under the neurosensory retina and in the vitreous.

Although the lesion can initially be mistaken for a melanoma, the diagnosis is confirmed by the formation of a typical, elevated scar in the involved area. Frequent fundus examinations are essential, and ultrasound, radioactive phosphorus uptake testing, and bilateral patching are helpful in establishing the diagnosis. The hemorrhage is usually the result of a ruptured vessel from a subretinal neovascular network or arteriosclerotic degeneration and may be precipitated by the use of anticoagulants.

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A VARIABLE FOCUS TELESCOPIC INSTRUMENT FOR INDIRECT OPHTHALMOSCOPY WITH INCREASED MAGNIFICATION AND STEREOPSIS

THOMAS A. POOLE, M.D., STANLEY POLER, M.S., AND R. DAVID SUDARSKY, M.D.
New York, New York

Giraud-Teulon[1] introduced stereoscopic indirect ophthalmoscopy in 1861; and Gullstrand[2] and others elucidated the optics of indirect ophthalmoscopy early in this century. The presently used instrument was popularized by Schepens[3] for the treatment of retinal detachment. Refinements have subsequently been suggested to increase magnification, stereopsis, and image quality.[4–6] We describe herein the design of a new binocular indirect ophthalmoscope and a complimentary examination technique that provides enhanced magnification and stereopsis through a wide range of patient pupillary apertures.

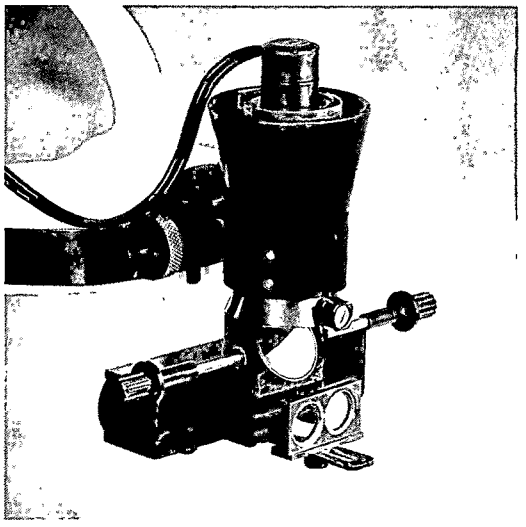


Fig. 1. (Poole, Poler, and Sudarsky). Photograph of the variable focus telescopic indirect ophthalmoscope, with the objective lens slide mid-extended to focus at about 40 cm.

MATERIAL AND METHODS

A variable focus binocular Galilean telescope of up to × 2.4 angular magnification has been incorporated into a Keeler indirect ophthalmoscope (Fig. 1). The ophthalmoscope eyepieces have been replaced by telescope ocular lenses. A pair of contiguous objective lenses has been mounted on a movable slide that allows the telescope to continuously focus 30 cm to 60 cm from the instrument (Fig. 2). The binocular telescope provides an erect, magnified image with a field of about 8 degrees. The optically reduced interpupillary distance of the original ophthalmoscope has been preserved.[1,7,8] The lightweight, mechanically simple system allows easy conversion between telescopic and standard viewing modes, if desired. Additional sets of interchangeable ocular and objective lenses allow one to use optimum magnification and field at a given viewing distance; however, they are not necessary for routine use of the instrument. Except for the reduced interpupillary distance and variable focus, the examiner's view when looking through the instrument is similar to that observed during use of surgical loupes.

For routine examination through dilated patient pupils, the objective slide is positioned to focus the ophthalmoscope at 30 cm to 40 cm (Fig. 2, left). Indirect ophthalmoscopy is performed in the usual way.[9] The enlarged, inverted, three-dimensional aerial fundus image provided by a given viewing lens is fur-

From the Department of Ophthalmology of the Manhattan Eye, Ear, and Throat Hospital, New York, New York. This study was supported in part by a grant from the Manning Foundation through the Eye Bank for Sight Restoration, Inc., New York, New York.

Reprint requests to Thomas A. Poole, M.D., 4 E. 77 St., New York, NY 10021.

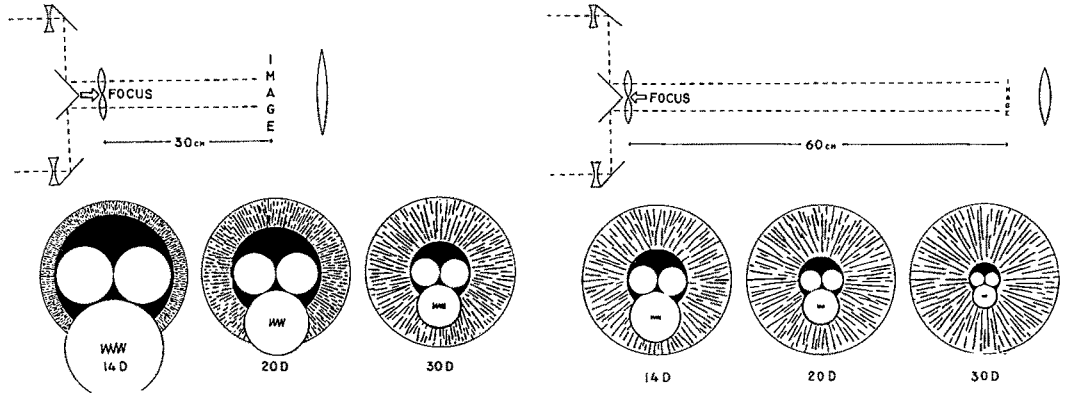


Fig. 2 (Poole, Poler, and Sudarsky). Schematic representation of the use of viewing lens distance and power variation to optimize stereopsis and magnification for a given pupillary aperture. Left, Variable focus telescopic ophthalmoscope focused on the viewing lens image at 30 cm (pupillary diameters: 8 mm, 6 mm, and 4 mm). Right, Variable focus telescopic ophthalmoscope focused on the viewing lens image at 60 cm (pupillary diameters: 4 mm, 3 mm, and 2 mm).

ther magnified about × 2.4 by the telescopic observation system of the ophthalmoscope. The observed fundus field of a given viewing lens remains the same, although a considerably greater magnification is achieved by using the telescope[4] (Fig. 3). This contrasts with the usual fundus magnification achieved by decreasing viewing lens power, which results in a marked reduction in observed fundus field because the longer focal length lens intercepts a smaller angular subtence of the rays emanating from the patient's pupil.[7] The standard aspheric viewing lenses are used to choose an appropriate (enhanced) fundus magnification.[6] For example, this ophthalmoscope design makes it possible to have the wide observed fundus field of a 30-diopter viewing lens while achieving a fundus magnification equivalent to that obtainable with a 14-diopter viewing lens and an ordinary ophthalmoscope.

The variable focus telescopic ophthalmoscope has a unique zoom focusing capability that makes indirect ophthalmoscopy considerably more convenient for the examiner. In practice, a working distance of 40 cm to 50 cm is frequently useful, allowing one to focus up or down on the image as desired by moving the viewing lens through the focusing range of the ophthalmoscope (30 cm to 60 cm). This maneuver creates a superimposed zoom magnification range of about × 2.6 with the present instrument, which considerably extends the magnification or small pupil penetrating characteristics of a given viewing lens. For example, the standard 30-diopter viewing lens used with the variable focus telescopic ophthalmoscope produces a range of fundus magnifications equivalent to using the 30-, 20-, and 14-diopter lenses with a standard ophthalmoscope. The instrument has a good depth of focus and can also be used in a static way without the zoom, similar to standard ophthalmoscopes, if the examiner chooses.

Increased fundus image magnification and stereopsis can be clinically valuable, particularly when examining lesions of the posterior pole. Even when using a 14-diopter viewing lens, the standard indirect ophthalmoscope does not have sufficient magnification and stereopsis to provide easy discrimination of fine retinal detail. The present variable focus tele-

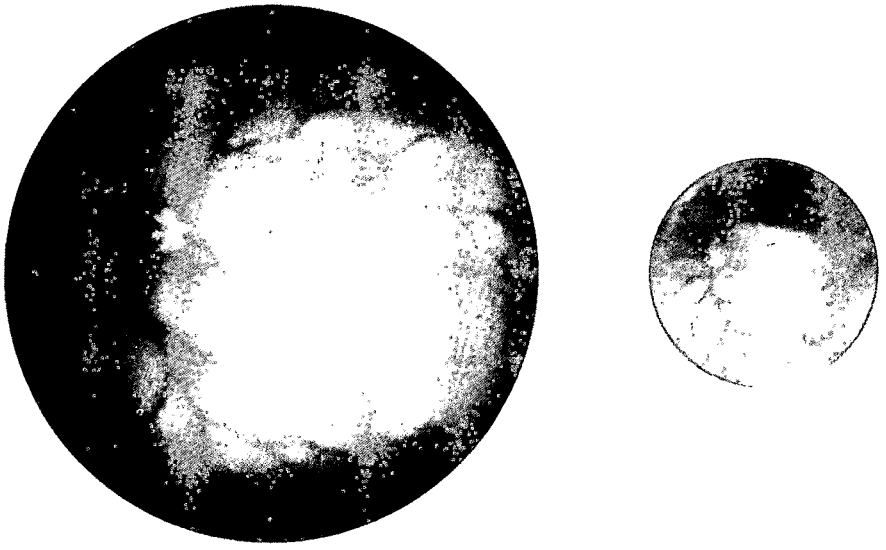


Fig. 3 (Poole, Poler, and Sudarsky). Photograph of a schematic eye as viewed through the variable focus telescopic indirect ophthalmoscope (left) and a standard indirect ophthalmoscope (right), demonstrating × 2.4 magnification with full retention of observed fundus field. The only variable in making the photographs was the Galilean telescopic observation system of the variable focus telescopic ophthalmoscope (20-D, 50-mm diameter condensing lens at 40 cm from the instrument used for both).

scopic ophthalmoscope increases the fundus magnification of a 14-diopter viewing lens image (viewed at 30 cm) to approximately × 8.5, which is sufficient for resolution of most retinal pathology. An 8-mm patient pupil is required for full binocularity in this situation. Focusing as close as possible to the image of a 14-diopter viewing lens while maintaining binocularity optically magnifies the separation of the imaged telescope entrance pupils, thus allowing optimum stereopsis for a given patient pupillary aperture[8,10] (Fig. 2, left). Increased magnification and stereopsis of the three-dimensional fundus image are the main reasons for the development of the variable focus telescopic indirect ophthalmoscope. Retinal lesions observed with this instrument appear to have thickness, and their level within the retina and pigment epithelium can be more easily localized. Some vignetting of the image field of a large lens viewed at 30 cm occurs when using the prototype instrument; however, this does not appear to be a significant clinical disadvantage because high magnification is useful mainly for localized areas of pathology. If the instrument is to be used primarily for high magnification viewing through widely dilated pupils, greater field or magnification can be obtained by changing the telescope lenses.

In the occasional extreme viewing situation presented by a miotic patient pupil, use of the instrument's variable focus capability greatly enhances visualization of the fundus. A 30-diopter or stronger viewing lens is useful for penetrating miotic patient pupillary apertures because the imaged observer pupils and illumination source are smaller and closer together than with viewing lenses of lesser power.[6,7] Holding the viewing lens as far from the ophthalmoscope as possible further enhances this effect (Fig. 2, right). Unfortunately, the fundus image ordinarily viewed while holding a 30-diopter or

stronger lens at arm's length is too small (magnification considerably less than × 1) to adequately visualize retinal detail because of reduction in angular magnification and because of the small aerial image formed by the strong viewing lens. The variable focus telescopic ophthalmoscope allows one to focus on a 30-diopter condensing lens image held at arm's length by sliding the telescope objective back to focus at approximately 60 cm (Fig. 2, right). The telescope then provides an increase in angular magnification sufficient to render the reduced aerial image adequate for visualization of retinal detail. Reduction of the size as well as separation of the imaged objective entrance pupils and light source sufficient to penetrate small patient pupillary apertures is accomplished optically by increasing the distance and power of the viewing lens, rather than by mirror adjustments within the ophthalmoscope itself.[5,6,8,10] The new instrument makes possible consistent visualization of the fundus through optically clear 2-mm pupils. Observed fundus magnification is about × 1.5 with the 30-diopter at 60 cm. Somewhat better small pupil penetrating capability can be obtained by changing the telescope lenses if the instrument is to be used mainly at a 60-cm or greater viewing distance. A useful ancillary point is that stereopsis becomes negligible with miotic patient pupils, no matter what type of ophthalmoscope is used. Therefore, occasional or partial loss of binocularity while imaging through a small pupil is not important if the retina can still be seen monocularly with adequate magnification.

Discussion

The variable focus telescopic ophthalmoscope is designed to maximize magnification and stereopsis for a given patient pupillary aperture. Magnification and stereopsis in indirect ophthalmoscopy are limited by patient pupillary diameter and by reduction of observed fundus image field.[7,8] A functional compromise between these opposing factors has been made in designing the variable focus telescopic indirect ophthalmoscope. The need to place the objective lenses (telescope entrance pupils) close enough together to achieve binocularity through the patient pupillary aperture and the need to maintain adequate fundus image field, brightness, and quality restrict the telescopic image magnification that can be practically used in this system to approximately that of the present prototype. To maximize magnification and stereopsis, one should generally use the condensing lens with the least dioptric power at the shortest distance from the ophthalmoscope that allows easy binocular imaging of the fundus. Penetration of small pupillary apertures is enhanced by the opposite maneuver: increasing viewing lens strength and distance from the ophthalmoscope. By varying the distance and power of the standard viewing lenses in conjunction with variable focus telescopic magnification, a continuous optimal adjustment to the size of the patient's pupil can be achieved (Fig. 2). The optical system of the present instrument is capable of about × 1.5 fundus magnification with negligible stereopsis in a 2-mm patient pupil, increasing to about × 8.5 with greatly increased stereopsis in an 8-mm pupil.

The combination of telescopic angular magnification with condensing lens distance (and power) variation is obviously desirable. It was a major consideration in designing this new instrument; however, the Galilean telescopic system makes excessive demands on the examiner's accommodation if he tries to vary his own focus through it. To eliminate this problem, variable focus capability is in-

corporated into the instrument design, eliminating the need for examiner accommodation. The variable focus telescopic ophthalmoscope is thus particularly advantageous for a presbyopic individual, who ordinarily requires additional plus lens power to focus on the fundus image through the standard ophthalmoscope. The Galilean system of the variable focus telescopic ophthalmoscope is afocal; light rays exiting from the system are parallel when the instrument is focused. To use the new ophthalmoscope with full viewing lens distance variation capability, the presbyope need only wear his distance correction (or incorporate it into the oculars). By manipulating the objective lens slide of the variable focus telescopic telescope, the presbyope acquires an artificial accommodation sufficient to visualize the magnified condensing lens image throughout the 30-cm to 60-cm focusing range of the instrument. (In Figure 3, the camera was focused at infinity through the variable focus telescopic ophthalmoscope and was focused at approximately 40 cm through the standard ophthalmoscope.)

Condensing lens distance variation can be used to a limited extent without the angular magnification and variable focus capability of the instrument presented; however, significant restrictions are imposed by demands on the unaided examiner's accommodation and acuity. An examiner who retains a good amplitude of accommodation should use the variable distance (and power) technique with the standard ophthalmoscope. It affords better magnification, stereopsis, and small pupil penetrating capability than is possible with a static technique, although the advantages of angular magnification provided by the variable focus telescopic ophthalmoscope are lacking. Many myopic examiners gain some additional magnification when using the standard instrument by removing their spectacles and focusing closer to the viewing lens image. Increases in magnification thus obtained are relatively limited, primarily because of loss of binocularity through the patient pupillary aperture.[7] The myopic observer is also unable to focus further than his own far point if he wants to penetrate a small patient pupillary aperture.

The observed brightness of the magnified fundus image of the variable focus telescopic ophthalmoscope is comparable to that of the standard indirect ophthalmoscope, with other variables being equal. The imaged entrance pupils of the telescope are larger than the imaged pupils of an unaided examiner using the standard instrument, and they therefore capture a considerably greater portion of the rays emanating from the patient's pupil (Fig. 2). The light-concentrating effect of the Galilean telescopic system effectively compensates for the reduction in brightness inherent in image enlargement. (The exposure factors used in making the photographs of Figure 3 were the same for both telescopic and standard images.) As with any ophthalmoscope, the brightness of the observed image is decreased with a miotic patient pupil.

Disadvantages of using the variable focus telescopic ophthalmoscope are related to Galilean optics, as might be expected. The instrument field of view is reduced in proportion to the magnification achieved; nevertheless, it is still generally adequate to completely visualize the fundus image of most standard viewing lenses (vignetting occurs with a large diameter lens at 30 cm using the present instrument). As with all indirect ophthalmoscopy, alignment of the instrument with the viewing lens must be precise, particularly when small pupil viewing is being performed. The variable viewing distance technique makes some demands on the examiner's vergences; it does not seem to be a problem when using the instrument.

The high magnification and optimum stereopsis of the variable focus telescopic ophthalmoscope have been particularly useful in observing the retinal small vasculature, in fluorescein angioscopy, in localizing pathology to levels within the retina and pigment epithelium, and in visualizing small retinal tears. Small pupil viewing is never easy, but it has been made more effective by use of the variable focus telescopic ophthalmoscope. Zoom magnification changes with a single viewing lens can add greatly to the convenience of indirect ophthalmoscopy. If desired, the lightweight, mechanically simple design allows easy conversion between telescopic and standard viewing modes. The instrument is only slightly more difficult to use than the standard indirect ophthalmoscope, and can be used with enhanced effectiveness as examiner sophistication improves. The variable focus telescopic ophthamoscope should prove of greatest value and interest to the experienced ophthalmoscopist who wants to extract maximum information from an examination.

Summary

We devised a new binocular indirect ophthalmoscope and a complimentary examination technique that provide enhanced fundus magnification and optimum stereopsis through a wide range of patient pupillary apertures. The lightweight, mechanically simple instrument uses a variable focus Galilean telescopic observation system to enlarge the condensing lens image of the fundus seen by the examiner. The present device is capable of about × 1.5 fundus magnification with negligible stereopsis through a 2-mm patient pupil, continuously increasing to × 8.5 with greatly enhanced stereopsis through an 8-mm pupil. A zoom focusing capability considerably extends the magnification, stereopsis, and samll pupil penetrating characteristics of a given condensing lens by allowing the examiner to binocularly observe the telescopically magnified fundus image throughout the 30-cm to 60-cm focusing range of the ophthalmoscope.

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A NEW FUNDUS LENS OPHTHALMODYNAMOMETER

MICHAEL E. YABLONSKI, M.D.
New York, New York

I have devised a new ophthalmodynamometer that may have several advantages over previously used devices. It consists of a Scherr Tumico stylus dynamometer modified by the attachment of a plastic ring, which is used in conjunction with a Haag-Streit fundus lens (Fig. 1).

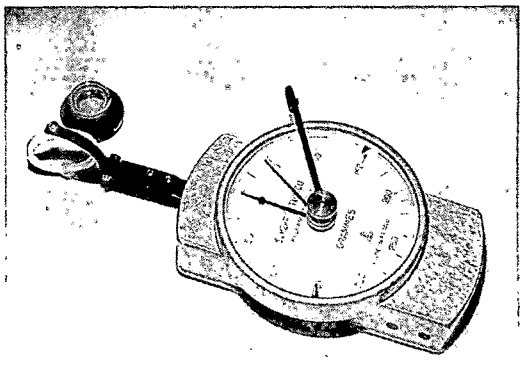


Fig. 1 (Yablonski). Dynamometer with plastic ring attached to stylus and fundus lens.

The device is used as follows: the pupils are dilated with a topically applied mydriatic, the cornea is anesthetized with a topically applied agent, and the fundus lens is applied to the cornea by using 2.5% hydroxypropyl methylcellulose. The disk is viewed through the fundus lens at the slit-lamp microscope, while the dynamometer is held in the hand of the examiner lateral to the eye, and the plastic ring is fitted over the lens (Fig. 2). While the ophthalmologist views the disk arteries through the center of the ring, he gradually applies force to the fundus lens until he sees the arteries on the disk begin to pulsate. The magnitude of the force required to produce this end point is determined by the indicator needle of the dynamometer, which reads the highest force reached during the measurement. As described by Weigelin and Lobstein,[1] the force required to produce artery pulsations on the disk is indicative of ophthalmic artery diastolic pressure, whereas the force required to cause cessation of artery pulsations is indicative of the systolic pressure.

In constructing the device, I sawed off the stylus tip of the dynamometer and attached the plastic ring so that its center coincided with the normal location of the stylus tip. A gimble permits rotation of the ring about the axis vertical to the stylus, allowing for some deviation of the dynamometer about this axis, while the ring remains flush with the fundus lens.

The lens must be centered on the cornea. The subject is instructed to look

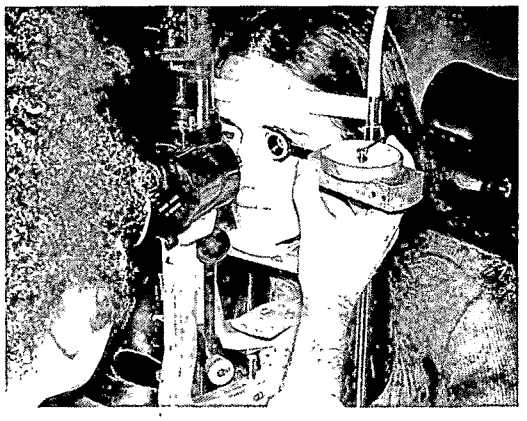


Fig. 2 (Yablonski). Use of the ophthalmodynamometer. The plastic ring is placed over the fundus lens and force is applied while viewing the disk arteries at the slit-lamp microscope.

From the Department of Ophthalmology, Mount Sinai School of Medicine of the City University of New York, New York, New York.

Reprint requests to Michael E. Yablonski, M.D., Department of Ophthalmology, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029.

slightly nasal to the slit-lamp light during the procedure. No fixation light is required. Because the stylus ring has a groove into which the fundus lens snugly fits, the examiner easily can keep the disk in view while applying force to the eye.

Diastolic readings are considered more reliable than systolic readings.[2] Hollenhorst[3] advised using "diastolic readings almost exclusively." In this study, only diastolic measurements were made.

Subjects and Methods

I tested the fundus lens ophthalmodynamometer in 60 normal adult volunteers. All subjects had intraocular pressures of 20 mm Hg or less with a difference between the two eyes of less than 2 mm Hg. Repeated readings were taken in each eye with a 60-second interval between readings until three consecutive readings were within ±10 g of each other. The average of the three readings was taken as the measurement for that eye. Usually, only three consecutive readings were required. Systemic blood pressure was measured by an assistant immediately before and after ophthalmodynamometry, and the two measurements were averaged. The examiner was unaware of the systemic blood pressure values during ophthalmodynamometry.

For comparison, in a similar group of 40 normal adult volunteers, Bailliart ophthalmodynamometry was done in a similar manner. In this case, repeated ophthalmodynamometry readings were continued until three consecutive values within ±5 g of each other were obtained.

To measure the effect of increased intraocular pressure on the fundus lens ophthalmodynamometry reading, I studied 18 subjects in whom the intraocular pressure of one eye was more than 20 mm Hg and more than 5 mm Hg higher than in the fellow eye. None of the patients in this group had visual field loss, pathologic optic disk cupping, or evidence of internal carotid disease. The procedure for this group was identical to that described above for the normal patients.

Results

In the normal volunteers, the mean value of the difference between the readings of the two eyes divided by the average reading of the two eyes using the fundus lens ophthalmodynamometer was .023 ± .033 (S.D.) compared to .064 ± .075 (S.D.) using the Bailliart ophthalmodynamometer. These two values were of significant statistical difference ($P<.01$).

The relationship between the individual average reading of the two eyes obtained by using the fundus lens ophthalmodynamometer and the systemic diastolic blood pressure is shown (Fig. 3). A correlation coefficient of 0.94 was obtained. The relationship between the Bailliart readings and systemic diastolic blood pressure is also shown (Fig. 3). In

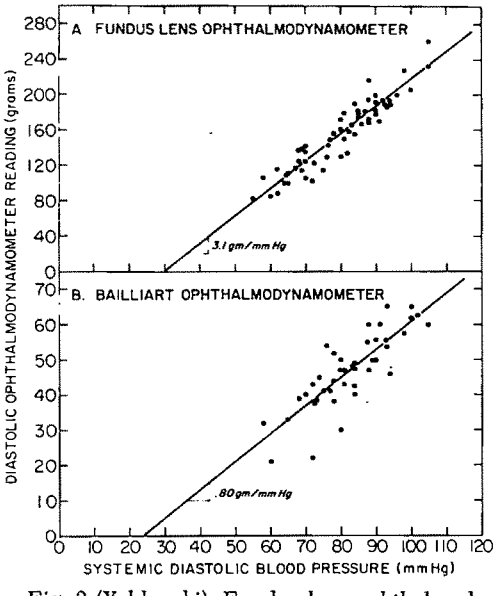


Fig. 3 (Yablonski). Fundus lens ophthalmodynamometer and Bailliart ophthalmodynamometer: average of the diastolic readings of the two eyes vs systemic diastolic blood pressure.

this study, the correlation coefficient was 0.83.

In the group in which the intraocular pressure of the two eyes was unequal, the mean ± S.D. of the difference in intraocular pressure was 12 ± 4.2 mm Hg. Using the fundus lens ophthalmodynamometer, the reading in the eye with the lower intraocular pressure exceeded the reading in the fellow eye by a mean ± S.D. of 15 ± 15 g ($P<.01$, paired t-test).

Discussion

Assuming that ophthalmic artery pressure should bear a linear relationship to systemic blood pressure,[4] I decided to test the new ophthalmodynamometer by correlating its diastolic reading with systemic diastolic blood pressure in normal subjects. The correlation was good (Fig. 3), indicating that the reading obtained was indeed a representation of ophthalmic artery pressure. Furthermore, the finding of only a 2.3% difference between the readings of fellow eyes showed good reliability of measurements.

Ophthalmodynamometry was not done successively in the same individuals with the fundus lens and Bailliart ophthalmodynamometers because it was not known to what extent testing with one device might influence the results obtained by the other. I thought that an adequate comparison could be achieved by comparing the results obtained in similar groups of normal volunteers. In my hands the fundus lens ophthalmodynamometer was superior to the Bailliart. The correlation between readings and systemic diastolic blood pressure was better with the fundus lens device (Fig. 3). Also, the mean difference between the readings of the two eyes was less with the fundus lens ophthalmodynamometer. A study is presently under way to compare the two devices in individuals with suspected internal carotid artery atherosclerosis.

Increase of intraocular pressure by a mean value of 12 mm Hg caused a statistically significant lowering of the fundus lens ophthalmodynamometry reading by a mean value of 15 ± 15 (S.D.) g; however, the effect was variable, as shown by the large standard deviation. Similar results have been reported by Goldstein, Peczon, and Cogan[5] by using the Bailliart ophthalmodynamometer.

The force required to reach the diastolic end point with the fundus lens ophthalmodynamometer is approximately 3.5 times that required with the Bailliart (Fig. 3). The different areas of contact with the globe are thought to account for this difference. The diameter of the area of contact using the fundus lens is 14 mm, compared to 7.3 mm with the Bailliart; therefore, the cross-sectional area of the former is 3.7 times as great. A force 3.7 times greater would be required with the fundus lens to exert the same pressure (force divided by area) on the globe. Other differences, undoubtedly, are also important in this regard. For example, the contact lens is concave and applied to the cornea, whereas the Bailliart footplate is convex and applied to the sclera.

Sisler[6,7] described a new ophthalmodynamometer, which was based on the principle of applying a measured force to a fundus lens. Unlike the device I describe, his instrument applied the force by means of a modifed slit-lamp mounted spring resistance tonometer. Sisler[6] compared the results obtained with this device and those obtained with the Bailliart and the suction type of ophthalmodynamometer in normal subjects. He found the fundus lens type to be superior to the other two.

The good correlation between the ophthalmodynamometer readings and diastolic blood pressure (Fig. 3) suggests possible uses greater than merely comparing the reading of one eye with that of the other, as is presently the common practice. No points fall more than 30 g below the line of best fit (Fig. 3). I am doing a

study to evaluate the instrument's ability to predict internal carotid artery atherosclerosis, as shown by arteriography, which shows that a reading falling more than 30 g below the line of best fit of Figure 3 is of comparable value to the finding of a difference of 15% or more between the readings of the two eyes (unpublished results).

This device appears to offer new possibilities in the field of ophthalmodynamometry. It is easily constructed and is inexpensive. The basic dynamometer is a sturdy, precision instrument, which can be purchased for about $50 from many machine and tool supply companies. The ring is easily attached to the stylus, and with only a little practice, the technique of using it is easily mastered.

Summary

I devised a new ophthalmodynamometer by means of which a measured force is applied to a fundus lens, while the disk vessels are viewed at the slit-lamp microscope. In my hands, the new device was superior to the Bailliart ophthalmodynamometer when tested in normal volunteers. With the fundus lens ophthalmodynamometer, the diastolic end point differed between the two eyes by a mean of 2.3%, compared to 6.4% with the Bailliart. The new device showed a better correlation with systemic diastolic blood pressure than did the Bailliart instrument. The effect of intraocular pressure on the reading with the fundus lens device was significant, although variable.

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SARCOIDOSIS AND ITS OPHTHALMIC MANIFESTATIONS

CARL D. OBENAUF, M.D., HAROLD E. SHAW, M.D., CHARLES F. SYDNOR, M.D., AND GORDON K. KLINTWORTH, M.D.

Durham, North Carolina

Sarcoidosis is an idiopathic, systemic, noncaseating, granulomatous disease with protean clinical manifestations. Although the first description of sarcoidosis is attributed to Hutchinson,[1] its ocular features received little attention until 1936 when Heerfordt's syndrome of uveitis, salivary gland enlargement, and cranial nerve palsies was recognized as a sign of sarcoidosis.[2] Subsequently, sarcoidosis was recognized as commonly affecting the eyes and ocular adnexae.[3–23] For a long time, there has been worldwide interest in this disease.[24,25]

Prompted by the high frequency of sarcoidosis in the southern United States, we conducted a retrospective study of a large series of such patients with emphasis on the ocular involvement.

MATERIAL AND METHODS

We reviewed the medical records of 767 patients admitted consecutively to the Duke University and Durham Veterans Administration Hospitals with suspected sarcoidosis between 1940 and 1974. Most patients were admitted between 1952 and 1974. We accepted the diagnosis of sarcoidosis when typical clinical, radiologic, laboratory, and, in most cases, histologic features of the disease were documented. Our criteria for diagnosis were based on the description of sarcoidosis proposed by the Seventh International Conference on Sarcoidosis and other Granulomatous Disorders,[24] which states:

> Sarcoidosis is a multisystem granulomatous disorder of unknown etiology, most commonly affecting young adults and presenting most frequently with bilateral hilar lymphadenopathy, pulmonary infiltration, skin or eye lesions. The diagnosis is established most securely when clinicoradiographic findings are supported by histological evidence of widespread noncaseating epithelioid-cell granulomas in more than one organ or a positive Kveim-Siltzbach skin test. Immunological features are depression of delayed-type hypersensitivity suggesting impaired cell-mediated immunity and raised or abnormal immunoglobulins. There may also be hypercalciuria, with or without hypercalcemia. The course and prognosis may correlate with the mode of onset: An acute onset with erythema nodosum heralds a self-limiting course and spontaneous resolution, whereas an insidious onset may be followed by relentless, progressive fibrosis. Corticosteroids relieve symptoms and suppress inflammation and granuloma formation.

We excluded from the study 235 cases in which the diagnosis of sarcoidosis was questionable, and all cases in which a causal agent was associated with the granulomatous inflammation. Of the remaining 532 acceptable cases of sarcoidosis, the diagnosis was supported by histologic examination in 497 (93.4%). Most of the tissue specimens were obtained from lymph nodes, skin, and liver biopsies. In 35 cases, there was overwhelming clinical evidence of sarcoidosis, but histologic examinations were not done. All of the 532 patients with sarcoidosis had eye examinations by physicians, and 377 (71%), including all of those with involvement of the eye, were examined by ophthalmologists.

RESULTS

Almost three fourths of the subjects in this series were black. Women were af-

From the Departments of Ophthalmology (Drs. Obenauf, Shaw, Sydnor, and Klintworth), and Pathology, (Dr. Klintworth), Duke University Medical Center, Durham, North Carolina. This study was supported in part by United States Public Health Service Grant 2 RO1 EY 00146 (Dr. Klintworth).

Reprint requests to Gordon K. Klintworth, M.D., Department of Pathology, Duke University Medical Center, Durham, NC 27710.

fected slightly more frequently than men. Seventy-five percent of the patients were less than 40 years of age (Table 1).

A variety of clinical manifestations heralded the development of sarcoidosis (Table 2). Many individuals were asymptomatic at the time of diagnosis, when abnormalities were detected on routine chest x-ray film examinations. Pulmonary, ocular, and constitutional symptoms, such as weakness, malaise, and weight loss were the most common manifestations of sarcoidosis in symptomatic cases. The first symptoms of the disease involved the eye in 101 patients. The following ophthalmologic abnormalities were evident when the disease first became clinically apparent: chronic granulomatous uveitis (65 cases), acute iritis with evidence of chronic ocular uveal lesions (21 cases), acute iritis (11 cases), unilateral proptosis caused by noncaseating orbital granulomas (two cases), unilateral proptosis caused by lacrimal gland enlargement (one case), and decreased vision caused by an elevated mass extending into the eye from the optic disk (one case). The latter lesion was found to be caused by extensive granulomatous inflammation at the time of enucleation. Almost all of these patients with ophthalmic symptoms had evidence of systemic sarcoidosis at the time of initial examination. Generally, those patients with acute iritis and fine keratic precipitates without other evidence of chronic ocular disease had a favorable course after therapy with corticosteroids.

TABLE 1

PATIENT CHARACTERISTICS

	No.	%
Race		
Black	385	72.4
White	143	26.9
Indian (American)	4	0.7
Sex		
Female	285	53.6
Male	247	46.4
Age at examination (yrs)		
0-9	1	0.2
10-19	107	20.1
20-29	188	35.3
30-39	103	19.4
40-49	72	13.5
50-59	34	6.4
60-69	23	4.3
>70	4	0.8

TABLE 2

MANIFESTATION OF SARCOIDOSIS AT FIRST EXAMINATION

	No.	%
Asymptomatic		
Abnormal chest x-ray film	192	36.1
Symptomatic		
Pulmonary	105	19.7
Ocular	101	19.0
Constitutional (weakness, malaise, weight loss)	86	16.2
Peripheral lymphadenopathy	48	9.0
Cutaneous	32	6.2
Arthralgias, arthritis	12	2.3
Central nervous system (Seizures, hypopituitarism, facial nerve palsies, meningitis)	10	1.9
Cardiac	2	0.4

Ninety-five percent of the patients had abnormal chest roentgenograms at the time that sarcoidosis was diagnosed. Most cases showed evidence of hilar lymphadenopathy with or without parenchymal infiltrates or fibrosis. Twelve cases had pleural effusions.

In virtually all cases, tuberculin skin tests and a variety of chemical analyses of the serum were performed. The latter included calcium, total protein, albumin, and globulin determinations. Tuberculin sensitivity was determined primarily by the Mantoux reaction using a purified protein derivative or old tuberculin antigen. The frequency of negative tubercu-

lin skin tests and abnormal serum protein and calcium at the time of diagnosis are summarized (Table 3). Less than 5% of patients had weakly positive tuberculin tests or developed positive reactions after initially negative reactions.

Sarcoidosis affected a variety of tissues. The systemic involvement of patients in this series was determined from the retrospective analysis of the recorded clinical examinations (Table 4).

Ocular involvement developed during the course of the disease in at least 202 cases (38% of patients seen by physicians; 54% of patients with formal ophthalmic examinations). Among the 385 blacks with sarcoidosis, the incidence of ocular involvement was 44.2%, whereas in the 143 whites, it was less frequent (21%). (These percentages are based on the total population of 532 cases of sarcoidosis examined by physicians.) No substantial differences were found in the age and sex characteristics between patients with and without ocular lesions. The systemic findings most commonly associated with ocular sarcoidosis are listed (Table 5).

The types of ocular abnormalities encountered were classified into three categories: (1) anterior segment disease, (2) posterior segment disease, and (3) orbital and other disease (Table 6). In the acute stage, the ocular inflammation was generally unilateral, and as the disease became chronic, bilateral involvement usually developed. Anterior segment structures were affected most often. Chronic granulomatous uveitis, exemplified clinically by mutton-fat keratic precipitates, iris nodules, and synechiae, was the most common ocular manifestation of sarcoidosis, occurring in slightly more than half of the patients with ocular involvement. Acute iridocyclitis, typified by ciliary injection, aqueous cells and flare, and

TABLE 3

LABORATORY RESULTS AT THE TIME SARCOIDOSIS WAS DIAGNOSED

	No.	%
Serum chemistry		
Serum protein abnormality	179	33.7
Albumin/globulin reversal	159	30.0
Total protein elevation	78	14.7
Hypercalcemia	69	13.0
Tuberculin skin tests		
Negative	509	95.7
Positive	23	4.3

TABLE 4

SYSTEMIC INVOLVEMENT IN SARCOIDOSIS

	No.	%
Intrathoracic		
Hilar adenopathy	371	70.(
Lung parenchyma	271	53.(
Extrathoracic		
Ocular	202	38.(
Peripheral lymphadenopathy	148	27.8
Cutaneous (includes erythema nodosum)	122	22.9
Hepatomegaly	118	22.(
Splenomegaly	69	13.(
Central nervous system	46	8.7
Musculoskeletal	38	7.2
Parotid	31	5.8
Cardiac	17	3.2
Other	27	5.1

TABLE 5

FINDINGS ASSOCIATED WITH OCULAR SARCOIDOSI

	No.	%
Abnormal chest x-ray film	187	92.(
Peripheral lymphadenopathy	58	28.7
Cutaneous lesions (including erythema nodosum)	57	28.2
Serum protein abnormality (Albumin/globulin reversal of increased total protein or both)	38	18.8
Hypercalcemia	34	16.8
Hepatomegaly	32	15.8
Central nervous system abnormality (Facial nerve palsy, hypopituitarism, meningoencephalitis, seizures)	26	12.9
Parotid gland enlargement	18	8.9
Splenomegaly	17	8.4

TABLE 6

ABNORMALITIES IN 202 PATIENTS WITH OPHTHALMIC SARCOIDOSIS

	No.	%
Anterior segment disease	171	84.7
Chronic granulomatous uveitis	106	52.5
Iris nodules	23	11.4
Acute iritis	30	14.9
Cataracts	17	8.4
Conjunctival lesion	14	6.9
Band keratopathy	9	4.5
Interstitial keratitis	2	1.0
Posterior segment disease	51	25.3
Chorioretinitis	22	10.9
Periphlebitis	21	10.4
Chorioretinal nodules	11	5.5
Vitreous cells, opacities, or both	6	3.0
Vitreous hemorrhage	3	1.5
Retinal neovascularization	3	1.5
Orbital and other disease	53	26.2
Lacrimal gland	32	15.8
Optic nerve	15	7.4
Motility	4	2.0
Orbital granuloma	2	1.0

sometimes fine keratic precipitates, but without evidence of chronic inflammation, was noted in 30 (14.9%) of patients with ocular disease. Cataracts, attributable to chronic inflammation or treatment with corticosteroids, conjunctival follicles or nodules, and band keratopathy also occurred. In this study, several cases with equivocal conjunctival abnormalities were excluded, but 14 patients had definite conjunctival follicles or nodules that could not be ascribed to another cause. Biopsies were done on four of these patients and were characterized by noncaseous granulomatous inflammation. Of the nine patients with clinically diagnosed band keratopathy, four manifested hypercalcemia; in the other patients, the serum calcium levels were normal. Schirmer tests and rose bengal staining were not done routinely in most cases. Thus, the incidence of keratoconjunctivitis sicca was not ascertained.

Posterior segment involvement was observed in about one fourth of the patients with ocular sarcoidosis (Table 6). Chorioretinitis, periphlebitis, and chorioretinal nodules were the lesions most frequently described. In only ten (4.9%) of the 202 cases was the posterior segment affected without the anterior segment being affected. The overall incidence of central nervous system involvement among the 532 cases of sarcoidosis was 8.7% (46), but of the 51 patients with posterior segment disease, the central nervous system was affected more than twice as often in ten (19.6%).

Lacrimal gland enlargement existed in 32 cases, 26 (81.3%) of whom were black patients. The enlargement was unilateral in eight patients, and bilateral in 24 cases. Biopsies disclosed granulomatous inflammation in three unilateral and five bilateral lacrimal gland enlargements. Of the nonbiopsied cases with bilateral lacrimal gland enlargement, parotid swelling was noted in seven cases; bilateral acute dacryoadenitis was diagnosed in one patient; and in two individuals, the enlarged lacrimal glands regressed while they were receiving systemic corticosteroids. The remaining nine patients had bilateral enlargement without other ocular manifestations of sarcoidosis.

A variety of lesions of the optic nerve and disk were noted: optic disk edema secondary to increased intracranial pressure (six cases), optic atrophy (four cases), papillitis (two cases), and retrobulbar optic neuritis (one case). Two patients had elevated masses extending intraocularly from the optic disk. An eye with one of these lesions was enucleated and was found to have extensive granulomatous inflammation of the optic nerve head.

Histologically confirmed orbital granulomas occurred in two patients with systemic sarcoidosis. Abnormal ocular motility secondary to involvement of the cranial nerves innervating the extraocu-

lar muscles ensued in four cases. An isolated third, fourth, or sixth cranial nerve palsy was detected in three patients. One individual had a combined third and fourth nerve palsy.

Glaucoma caused by the inflammation was observed at some time during the course of the disease in 22 patients (10.9% of patients with ocular sarcoidosis). Of these, three (13.6%) developed advanced glaucomatous cupping of the optic disk. Eleven patients (all black) became blind secondary to ocular lesions, generally caused by chronic uveitis, with six cases eventually developing phthisis bulbi. Eight patients, representing 4% of those with ocular sarcoidosis, eventually required enucleation.

Discussion

Sarcoidosis concerns physicians of virtually all specialties. It is particularly important to the ophthalmologist since a significant number of patients will seek initial medical examination because of ocular disease. Considering clinically detectable lesions, we found only hilar lymphadenopathy and pulmonary abnormalities to be more common than ophthalmic manifestations. Clearly, all patients with suspected sarcoidosis deserve a thorough ophthalmologic examination. Conversely patients with ocular findings suggestive of sarcoidosis should be examined for systemic disease. The single most important screening test is the chest x-ray film examination, which in our series was abnormal in more than 18 +(90%) of the patients with ocular sarcoidosis. Because of this, we recommend that all patients with acute or chronic uveitis should have an x-ray film examination of the chest as part the clinical examination. Biopsy of accessible appropriate tissues, such as skin or lymph nodes, is essential for diagnosis. The intradermal Kveim-Siltzbach test is reportedly positive in 80% of sarcoidosis patients, but the lack of a standardized test material has limited its usefulness.[25]

A recent review of sarcoidosis around the world revealed ocular involvement in 11 to 32% of cases.[25] In the largest single survey of 442 cases previously reported,

TABLE 7

INCIDENCE OF OCULAR MANIFESTATION AND INVOLVEMENT IN PATIENTS WITH SARCOIDOSIS IN DIFFERENT REGIONS*

Country	City	No. of Patients	Ocular Examination		Ocular Involvemen	
			No.	%	No.	%
United States	Durham	532	101	19	202	38
	New York	311	22	7	62	20
	Los Angeles	150	15	10	17	11
Britain	London	537	53	10	147	27
	Reading	425	30	7	69	16
	Edinburgh	502	32	6	53	11
France	Paris	350	29	9	37	11
Italy	Naples	624	3	0.4	3	0.4
Japan	Tokyo	282	63	22	91	32
Spain	Lisbon	89	2	2	5	6
Switzerland	Geneva	121	9	8	15	12
Yugoslavia	Novi Sad	285	11	4	43	15

*Modified from James and associates.[15]

James and associates[15] found 27.8% of patients to have ophthalmic manifestations. In our study the frequency of ocular involvement was higher than previously documented. The true incidence in the present series is difficult to assess, but it probably lies somewhere between 38% (Table 7) (the incidence in patients examined by physicians who would probably overlook subtle lesions) and 54% (the incidence in a selected population of patients referred for formal ophthalmic examination). As shown in this study and by others, anterior or segment structures are affected more frequently than other parts of the eye or its adnexa in patients with sarcoidosis. In our review, the eyes and their adnexa were affected more than twice as often in blacks than in whites. No individual ophthalmic abnormality could account for this racial predominance of ocular sarcoidosis. A higher incidence of secondary glaucoma, blindness, and subsequent enucleation also occurred in blacks. This can be explained, at least partly, by several factors unrelated to the disease process. A delayed visit to the physician for treatment and a failure to adhere to medical regimen was more common in blacks than in whites. This was the case in five of the 11 cases in which patients developed blindness. Thus, the prognosis is less favorable in those patients who delay their medical care.

The true incidence of conjunctival involvement in sarcoidosis is difficult to ascertain. James and associates[15] reported conjunctival involvement in 23.6% of patients with ocular sarcoidosis, but they included a variety of nonspecific abnormalities. We excluded conjunctival reactions that are often coincidental to sarcoidosis, but nevertheless found the conjunctiva to be affected clinically in 14 (6.9%) patients with ocular sarcoidosis. Because the conjunctival biopsy is a safe, simple procedure, it has been advocated for the diagnosis of sarcoidosis, even in the absence of clinically apparent conjunctival lesions. Although conjunctival biopsy was not routinely performed in this series of patients, other researchers have demonstrated its value in cases of suspected sarcoidosis. The diagnostic yield from such a procedure has varied considerably. Crick, Hoyle, and Smellie[10] obtained a positive conjunctival biopsy in 14% (19) of 139 patients with sarcoidosis. Bornstein, Frank, and Radner[4] found the procedure decisive in 16 (25%) of their 64 patients with confirmed or suspected sarcoidosis. More recently, Khan and associates[19] reported a 33% (20 patients) incidence of positive conjunctival biopsies in 60 patients with histologically confirmed sarcoidosis, irrespective of the presence or absence of visible ocular lesions.

The predominant posterior segment manifestations of sarcoidosis in the present study as well as in Gould and Kaufman's[12] review of 40 cases of fundus sarcoid, were chorioretinitis and retinal periphlebitis. The chorioretinitis is clinically indistinguishable from that caused by other factors.[12] Retinal periphlebitis, producing the ophthalmoscopic appearance of "candle-wax drippings" in the more severe cases, is a hallmark of the disease. This finding, though not pathognomonic,[6] suggests the diagnosis of sarcoidosis. Variable-sized yellowish white to waxy chorioretinal nodules, frequently noted in this series, have been discussed by others.[12,15,22] Vitreous opacities were first described by Landers[20] as characteristic grayish white bodies frequently found in the inferior vitreous and occurring in chains like a "string of pearls."[20,22] Although uncommon in this review, cells and opacities have been reported in the vitreous in 30% of cases with fundus sarcoid in one series,[12] and in all 13 patients with such manifestations in another.[9] When the posterior segment is

affected in sarcoidosis, the anterior portion of the eye is usually also involved. However, as emphasized by our review and others, retinopathy may be the sole ophthalmic expression of the disease.[22]

Our study also demonstrates that posterior segment sarcoidosis is commonly accompanied by involvement of the central nervous system. Our finding that the brain was affected in about one fifth of cases with posterior segment disease is lower than the 35% incidence reported by Gould and Kaufman,[12] but stresses the need for a thorough neurologic examination in patients with this form of ocular sarcoidosis. Optic nerve involvement in sarcoidosis is usually manifested by papilledema, papillitis, optic neuritis, and rarely by granulomas of the optic disk.[5,11,17,18,21] When sarcoidosis affects the brain, the intracranial portion of the optic nerve may be involved by the inflammatory reaction.

Lacrimal gland involvement in sarcoidosis is well established.[7,8] Its incidence in this series was higher (32 [15.8%] of 202 cases) than the seven (5.7%) of 123 cases reported by James and associates.[15] This discrepancy may partly reflect a subjective interpretation of different observers, particularly in blacks in whom normal lacrimal glands in shallow orbits may be so prominent that they appear enlarged. Only nine of the 32 cases demonstrated bilateral lacrimal enlargement as the sole ophthalmic manifestation of sarcoidosis. The remaining patients were found to have either unilateral lacrimal enlargement, associated parotid swelling, histologic verification of granulomatous inflammation in the lacrimal gland, or the lacrimal glands diminished in size with corticosteroid therapy. Orbital involvement is a rare cause of unilateral proptosis.[26,27] Sometimes orbital masses are excised, which on histopathologic examination resemble the lesions of sarcoidosis, but occur in the absence of other systemic evidence of this disease. Although some regard such lesions as examples of isolated sarcoidosis, this interpretation is open to question.

James and associates[15] emphasized certain well defined clinical syndromes of ocular sarcoidosis, namely, that patients with acute iritis, erythema nodosum, and hilar lymphadenopathy tend to have a benign self-limiting course, whereas those individuals with chronic uveitis, skin plaques, pulmonary fibrosis, and bone cysts respond poorly to treatment with corticosteroids and almost invariably have a prolonged, complicated course. Corticosteroids are usually effective in the treatment of ocular sarcoidosis. Unfortunately, some cases progress to blindness despite therapy. However, early recognition and treatment of ocular sarcoidosis may prevent serious ocular damage. The acute iridocyclitis usually resolves without sequelae, but chronic lesions may cause serious ocular morbidity and even blindness. Sarcoidosis involving the posterior segment has a variable course, but from the standpoint of producing visual impairment, it is usually of secondary importance compared to disease in the anterior portion of the globe.

Summary

Of 532 cases of sarcoidosis in the southeastern United States, ocular manifestations were a prominent feature of the disease in 202 (38%) of the patients. Approximately one fifth of them sought medical attention because of ocular complaints. This was the second most frequent clinical manifestation, exceeded only by pulmonary symptoms. When ocular segment structures were affected, the anterior segment was involved in 171 (84.7%) of cases. Chronic granulomatous uveitis was the most common abnormali-

ty in 106 cases (52.5%). Posterior segment disease occurred in 51 (25.3%) of cases, usually in the form of chorioretinitis or preiphlebitis; it was sometimes the sole manifestation of ocular sarcoidosis, but usually accompanied abnormalities in the anterior part of the eye. The incidence of central nervous system sarcoidosis was increased when posterior segment involvement was observed. Orbital and adnexal structures, primarily lacrimal gland, were affected in 53 (27.7%) of cases.

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INTRACRANIAL SARCOIDOSIS WITH OPTIC TRACT AND TEMPORAL LOBE INVOLVEMENT

EUGENE B. MCLAURIN, M.D.
Oakland, California

AND

DAVID O. HARRINGTON, M.D.
San Francisco, California

Sarcoidosis, a common idiopathic granulomatous disease, has been known for more than 70 years to affect the central nervous system.[1] Over the past two decades, neurologic sarcoidosis has been recognized with increasing frequency,[2] and the incidence of the neurologic manifestations of the disease has been reported to be from 1%[3] to a high of 29%.[4] The overall frequency of neurologic sarcoidosis is about 5%.[5]

We report herein a unique case which demonstrates a right homonymous hemianopic visual field defect, radiographic evidence of intracranial sarcoid lesion by computed axial tomography, radiographic signs of pulmonary sarcoidosis by chest x-rays, and a positive pulmonary hilar lymph node for sarcoid. Treatment with large doses of prednisone resulted in symptomatic and radiographic improvement, and partial resolution of the visual field defects.

CASE REPORT

A 23-year-old man was examined initially on April 4, 1976, with a one-month history of pain and blurring of vision in both eyes. Examination revealed corrected visual acuity of 6/9 (20/30) in each eye, pupils were equal, round, and reactive to light, there was no Marcus Gunn pupil, and muscle movements were normal. Intraocular pressure by applanation was 12 mm Hg in the right eye and 15 mm Hg in the left eye. Both eyes showed moderate flare and cells in the anterior chamber. Anteroposterior and lateral chest x-rays revealed marked bilateral hilar and paratracheal adenopathy (Fig. 1), which is characteristic of pulmonary sarcoidosis. There were no pulmonary symptoms. Diagnosis was uveitis associated with pulmonary sarcoidosis.

On June 6, 1977, the patient returned complaining of photophobia and decreased vision. Corrected visual acuity was R.E.: 6/12 (20/40) and L.E.: 6/15 (20/50). Visual fields were done by the confrontation method and were normal. Several mutton-fat keratic



Fig. 1 (McLaurin and Harrington). Chest x-ray revealing bilateral hilar and paratracheal adenopathy typical of pulmonary sarcoidosis.

From the Department of Ophthalmology, University of California, San Francisco, California (Dr. Harrington), and the Naval Regional Medical Center, Oakland, California (Dr. McLaurin). The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy or the Department of Defense.

Reprint requests to Eugene B. McLaurin, M.D., Department of Ophthalmology, Naval Regional Medical Center, Oakland, CA 94627.

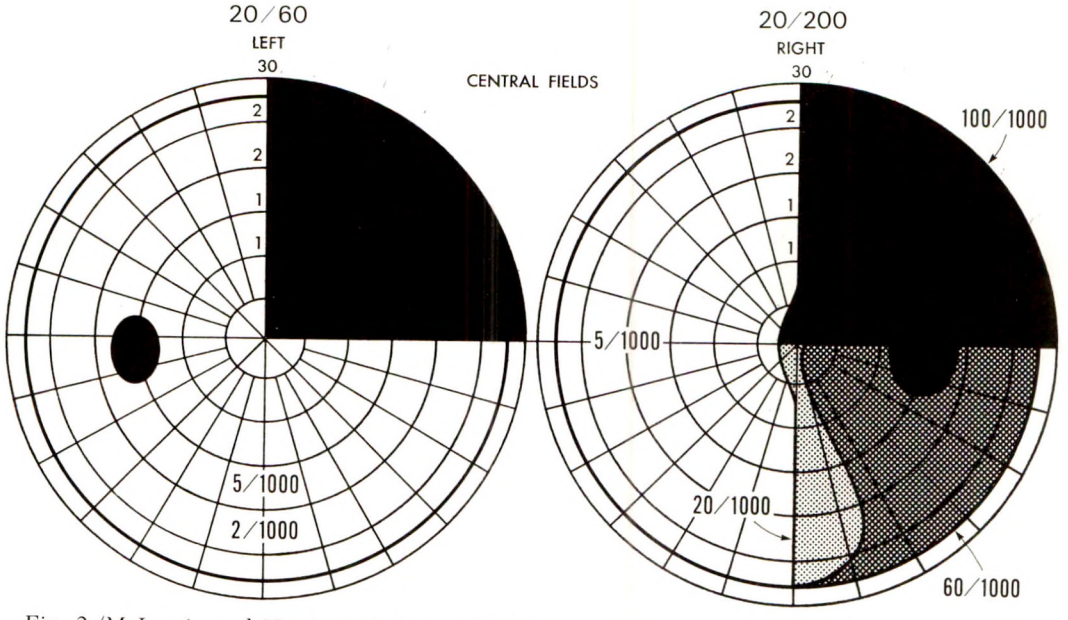


Fig. 2 (McLaurin and Harrington). Visual fields showing an incongruous homonymous hemianopia characteristic of optic tract and temporal lobe lesions.

precipitates were present in both eyes. The patient's uveitis responded to treatment with topical prednisone and atropine.

On Aug. 23, 1977, the patient reported a two-week period of blurred vision in the right eye. Visual acuity when corrected was reduced to 6/60 (20/200) in the right eye and 6/18 (20/60) in the left eye. Intraocular pressure measured 13 mm Hg in each eye. The anterior chamber was clear and the results of ophthalmoscopic examination were normal. Visual field studies on the tangent screen revealed a markedly incongruous right homonymous superior quadrantanopia with sloping margins, even to large stimuli (Fig. 2). Pupils were equal and round, reactive to light, and there was no Marcus Gunn pupil. Except for the visual field defect, the results of a neurologic examination were normal and there were no abnormalities evident on the anteroposterior, lateral, and stereoscopic views of the skull x-rays. The anteroposterior and lateral chest x-rays had not changed from those of April 1976.

Computed axial tomography indicated a large lesion in the suprasellar cistern with posterior extension into the medial portion of the left temporal lobe, along the left optic tract (Fig. 3). The patient was hospitalized for further studies including a search for other neurologic defects. Blood studies were all normal including calcium, phosphorous, alkaline phosphatase, glucose, serum glutamic oxaloacetic transaminase, and lactate dehydrogenase. The patient refused to allow a lumbar puncture to be performed. Pulmonary function tests revealed a mild pulmonary obstructive disease consistent with that of a smoker. The patient smoked a pack of cigarettes a day. He was discharged from the hospital with a diagnosis of pulmonary sarcoidosis and intracranial involvement. Treatment consisted of 80 mg of oral prednisone daily, and at two-week intervals a complete ophthalmic examination, including visual field studies, was performed.

By Oct. 31, 1977, there was marked improvement in the right superior homonymous quadrantanopia with widening of the area of the macular sparing and decrease in the incongruity of the defect (Fig. 4). Corrected visual acuity improved to 6/19 (20/30) in each eye. Repeat computed axial tomography showed complete resolution of the left temporal lobe lesion and the suprasellar mass had disappeared, except for a small focus of increased attenuation just lateral to the third ventrical (Fig. 5). The anteroposterior and lateral chest x-rays showed a decrease in the pulmonary lesions (Fig. 6). At this point the patient received 40 mg of oral prednisone every other day, which was slowly decreased over a two-month period of time.

The patient was admitted to the hospital on April 3, 1978, for mediastinoscopy to establish a tissue diagnosis of sarcoidosis. Biopsies were done on several mediastinal lymph nodes, and the frozen and permanent section was consistent with sarcoidosis.

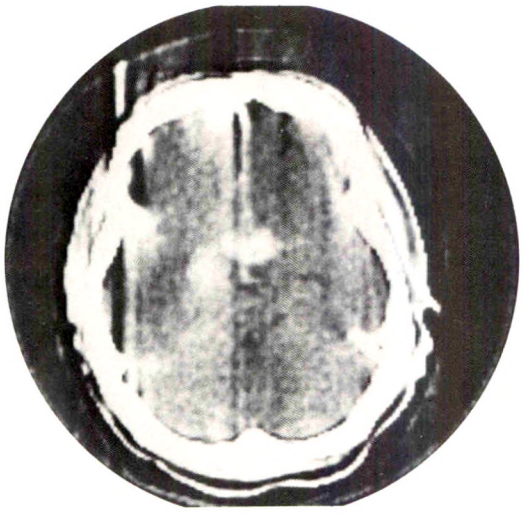


Fig. 3 (McLaurin and Harrington). Computed axial tomography showing large lesion in the suprasellar cistern with extension into the left temporal lobe along the left optic tract.

Discussion

The central nervous system is not a common site for lesions of sarcoidosis, but Delaney,[5] recently reviewed over 400 cases which had a 5% overall frequency of neurologic involvement. Most patients were between 20 and 40 years old, and racial distribution was primarily black. Central nervous sytem involvement was evident early in the disease, and the peripheral nervous system and skeletal musculature were involved in the late or chronic stages. About 20 cases of sarcoid were initially diagnosed as brain tumors.[6–11] A radioisotope study done by Rosen and Wang[9] included a patient with intracranial and pulmonary involvement of sarcoid that improved with corticosteroid therapy.

Visual disturbances with sarcoidosis are usually related to uveitis. Visual field defects have rarely been reported. Lawrence[2] described a patient with a left homonymous superior quadrantanopia with subsequent visual field contraction caused by sarcoid. A biopsy of the right optic nerve was consistent with sarcoid. Another patient[8] had a right homonymous

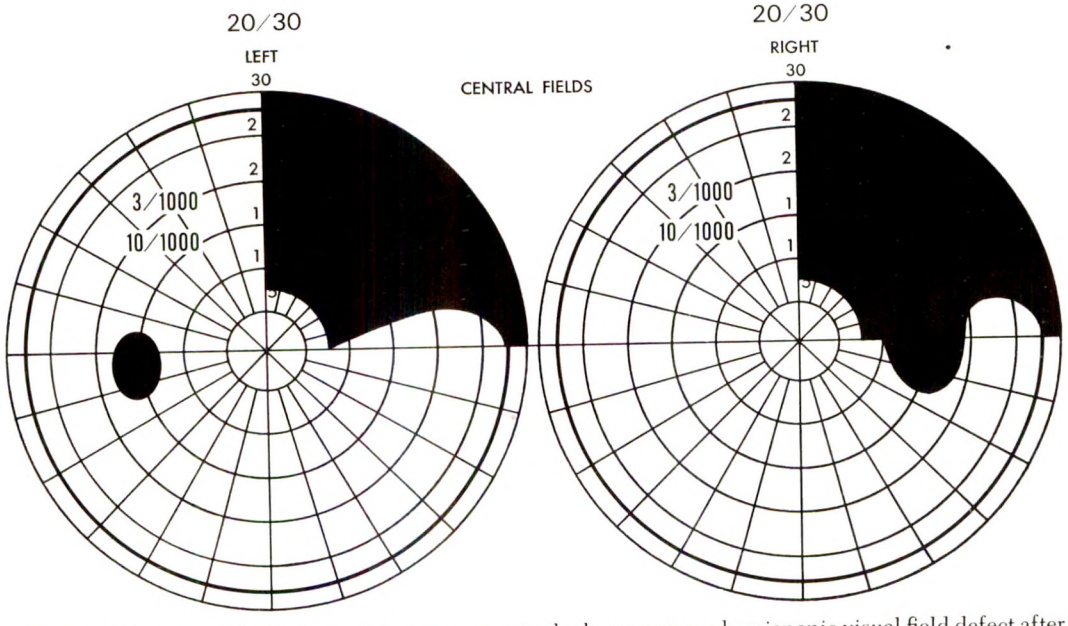


Fig. 4 (McLaurin and Harrington). Improvement in the homonymous hemianopic visual field defect after prednisone therapy.

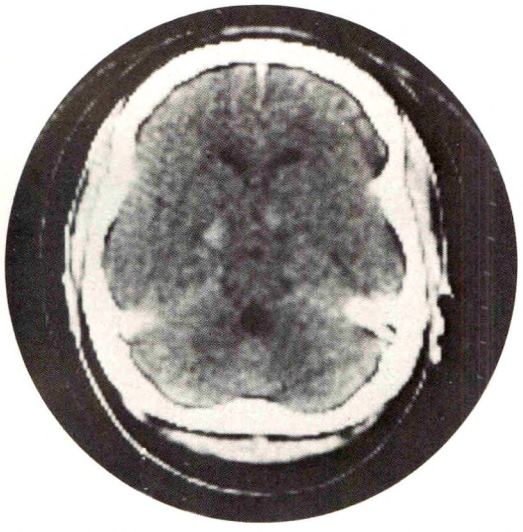


Fig. 5 (McLaurin and Harrington). Computed axial tomography after prednisone therapy showing almost complete resolution of the left temporal lesion and the suprasellar mass demonstrated in Figure 3.

hemianopia caused by a large sarcoid lesion in the left occipital lobe. A third patient[12] had involvement of the chiasm with bitemporal hemianopia and x-ray evidence of changes in the sella turcica.



Fig. 6 (McLaurin and Harrington). Chest x-ray showing decrease in the pulmonary lesions shown in Figure 1.

Intracranial sarcoid lesions are most commonly found in the hypothalamus, the region of the third ventricle, and the pituitary gland.[6,13] The normal sarcoid granuloma rarely shows calcification in x-ray studies of the skull.[14]

With corticosteriod therapy, the disease may remain in remission for considerable periods of time, but usually recurs when the dosage is decreased. Several of Delaney's[5] patients showed dramatic improvement in their neurologic deficits while under treatment. Other patients responded poorly or not at all.

In view of the serious neurologic involvement, we think all patients with intracranial sarcoidosis should receive intensive corticosteroid therapy.

Summary

Intracranial sarcoidosis was diagnosed in a 23-year-old man when he developed a markedly incongruous right homonymous hemianopic visual field defect. The diagnosis was substantiated by radiologic evidence of bilateral hilar and paratracheal adenopathy, typical of pulmonary sarcoidosis. Subsequently, computed axial tomography indicated a large intracranial lesion in the suprasellar cistern with extension into the left temporal lobe along the optic tract. A mediastinal biopsy of the lymph nodes was positive for sarcoid. Intensive corticosteroid therapy resulted in restoration of vision, marked improvement of the visual field defect, decrease in the pulmonary hilar adenopathy, and almost complete resolution of the left temporal lobe lesion.

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OPHTHALMIC MINIATURE

. . . He was plainly blind, for he tapped before him with a stick, and wore a great green shade over his eyes and nose; and he was hunched, as if with age or weakness, and wore a huge old tattered sea-cloak with a hood that made him appear positively deformed. I never saw in my life a more dreadful-looking figure. He stopped a little from the inn and, raising his voice in an old sing-song, addressed the air in front of him:

"Will any kind friend inform a poor blind man, who has lost the precious sight of his eyes in the gracious defense of his native country, England, and God bless King George!—where or in what part of this country he may now be?"

Robert Louis Stevenson
Treasure Island

MENINGEAL CARCINOMATOSIS WITH BLINDNESS

RICHARD E. APPEN, M.D., GUILLERMO DE VENECIA, M.D.,
JOSEPH H. SELLIKEN, M.D., AND LAURENCE T. GILES, M.D.
Madison, Wisconsin

Meningeal carcinomatosis, a diffuse infiltration of the meninges by metastatic tumor cells, has been recognized since the early 1900s.[1-5] Fischer-Williams, Bosanquet, and Daniel[1] and Katz, Valsamis, and Jampel[3] emphasized the frequent occurrence of visual loss in 30 to 40% of patients with this disorder, although more recent reports[5,6] suggest a less common association. We describe herein the clinical and histopathologic findings in a patient whose blindness was a prominent manifestation of meningeal carcinomatosis.

CASE REPORT

A 53-year-old man was admitted to Madison General Hospital on May 30, 1976, because of nausea, vomiting, and hematemesis. Upper gastrointestinal x-ray films and esophagoscopy were unremarkable, as were x-ray films of the chest and skull. Several days later, psychiatric deterioration, considered an exacerbation of his long-standing schizophrenia, resulted in a brief discharge from the hospital and readmission to the psychiatric service on June 12, 1976.

He had had intermittent schizophrenic episodes for 20 years, and peptic ulcer disease had been documented 18 years before admission. The patient had smoked one-half pack of cigarettes daily from 18 to 50 years of age.

On examination, the patient was disheveled and restless. Blood pressure was 156/94, and he was afebrile. The neurologic examination showed that he was disoriented to time, place, and situation. His level of alertness varied markedly from hour to hour, and he could not perform "serial 7" subtractions. Cranial nerves, muscle strength, sensation, and deep tendon reflexes were normal. His neck was supple. The gait was ataxic. On neuro-ophthalmologic examination (June 24, 1976), visual acuity was 6/6 (20/20) in each eye. Ocular motility, pupils, visual fields, anterior segments, and intraocular pressure were normal. The right optic disk was flat, had good color, and contained a hemorrhage at the superior pole. The left disk was normal. Blood tests showed slightly increased fasting glucose level (136 mg/100 ml), but normal studies included complete blood cell count, platelet count, erythrocyte sedimentation rate, T-3, T-4, and serum concentrations of calcium, phosphorus, hepatic enzymes, and ammonia. Urine was normal or negative for heavy metals, arsenic, and porphyrins.

Roentgenograms of the skull and technetium Tc 99m brain scan were normal. An electroencephalogram showed diffuse slowing of the background activity. Computed axial tomography scan revealed dilation of all ventricles, suggestive of communicating hydrocephalus. Radio-iodinated serum albumin scans from the lumbar approach (June 15 and 21, 1976) produced no radioactivity above the foramen magnum, but following a cisternal tap (June 24, 1976), the study was normal, indicating normal flow and absorption of the cerebrospinal fluid. The initial lumbar puncture revealed marked variation in opening pressure from 320 to 540 mm H_20. The cerebrospinal fluid contained 562 red blood cells per milliliter and 36 white blood cells per milliter with a differential count of 89% lymphocytes, 7% polymorphonuclear keukocytes, and 4% "others." The spinal fluid contained 118 mg/100 ml of protein and 22 mg/100 ml of glucose. The gamma globulin was 8% and VDRL was nonreactive. Stains and culture for bacteria, acid-fast bacilli, and fungi were negative.

Bilateral carotid and left brachial arteriograms (June 17, 1976) were normal. Pneumoencephalogram (July 13, 1976) showed a uniformly enlarged ventricular system without evidence of a mass.

Two weeks after the second admission, the patient became more agitated and required restraints. Following treatment with haloperidol, he became more alert and cooperative. However, on July 1, 1976, he developed increased headache, meningismus, and vomiting. On July 5, the patient had hyporeflexic quadriparesis and intermittent seizures began. On July 7, he was confused, febrile, and quadriparetic, and he indicated that he was essentially blind. Although at times he claimed to have some vision, he could not consistently identify the presence of a flashlight. The pupils were unreactive to light. The fundi were normal, and the previously noted optic disk hemorrhage had been absorbed.

Repeat lumbar puncture revealed an opening

From the Department of Ophthalmology, University of Wisconsin Hospitals (Drs. Appen and de Venecia), and the Departments of Pathology (Dr. Selliken) and Medicine (Dr. Giles), Madison General Hospital, Madison, Wisconsin. This work was supported in part by Grant No. EY 00039 from the National Eye Institute.

Reprint requests to Richard E. Appen, M.D., Department of Ophthalmology, University of Wisconsin Hospitals, 1300 University Ave., Madison, WI 53706.

pressure of 200 mm H_2O, 1 white blood cell per milliliter, protein concentration of 127 mg/100 ml, and glucose concentration of 50 mg/100 ml.

Then, remarkably, on July 9, he became more alert and responsive with fluent, lucid speech. The quadriparesis and blindness persisted, however. At the time of the pneumoencephalogram on July 13, cells were seen in the cerebrospinal fluid that were suspected to be malignant. However, oncology, radiotherapy, and tumor board consultants concluded that malignant intracranial disease had not been proven, and antineoplastic therapy was not administered.

The subsequent course was striking in that times of marked deterioration (July 5, 20, and 29, and August 16) were separated by times of improvement when the patient became oriented, communicative, and even jocular. The visual function, however, remained profoundly impaired. In late August, he became persistently stuporous, and he died 2½ months after admission to the hospital. General autopsy and ocular and cerebral examination, including the entire visual pathways, were performed.

RESULTS

Postmortem examination—At general autopsy, the lungs revealed in the right upper lobe a 1.5-cm mass impinging on the lumen of a bronchus (Fig. 1). Microscopically, the tumor consisted of pleomorphic cells containing abundant cytoplasm and hyperchromatic nuclei with occasional mitotic figures. The cells were frequently arranged in acini and represented pulmonary adenocarcinoma (Fig. 2). Metastases were present in the liver, spleen, adrenal glands, kidneys, and one lymph node.

The brain weighed 1,300 g. The only gross external abnormality was mild thickening and clouding of the pia and arachnoid. The optic nerves and occipital lobes appeared normal externally. Microscopically, there was diffuse infiltration of the pia and arachnoid and of the choroid plexus by the metastatic carcinoma, but no invasion of the cortex itself. The meningeal carcinomatosis extended into the spinal canal and involved multiple nerve roots.

Ocular and optic nerve histopathology—On gross examination the eyes appeared normal. After being placed in 10% buffered formalin solution, they were sectioned in the vertical plane. Paraffin sections were stained with hematoxylin and eosin and with PAS reagents. Microscopi-



Fig. 1 (Appen and associates). Right lung reveals a 1.5-cm mass (arrow) adjacent to a bronchus.

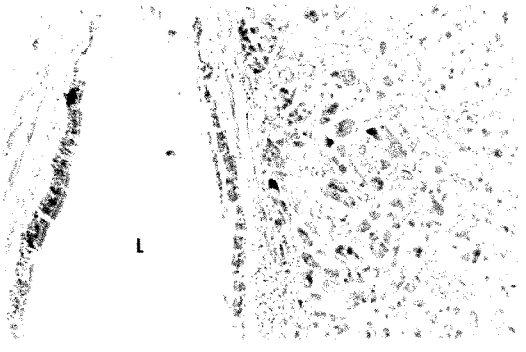


Fig. 2 (Appen and associates). Microscopic appearance of the pulmonary nodule adjacent to bronchus (L, lumen of bronchus). The pleomorphic tumor cells contain abundant eosinophilic cytoplasm and hyperchromatic nuclei, characteristic of adenocarcinoma (hematoxylin and eosin, ×32).

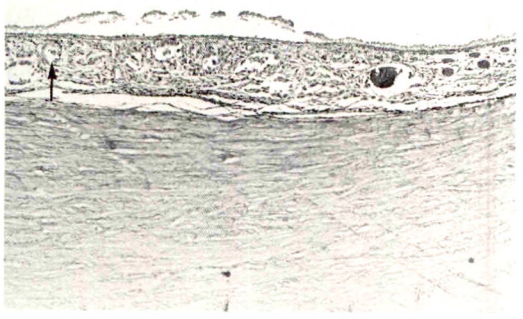


Fig. 3 (Appen and associates). Choroid of right eye thickened by metastatic adenocarcinoma. Arrow indicates acinus formation (hematoxylin and eosin, ×16).



Fig. 4 (Appen and associates). Right optic nerve (27-mm segment) shows normal myelin stain. Solid arrows indicated filmy arachnoid layer, and open arrows the denser dura layer at the distal end (D) of optic nerve. Toward the proximal end (P) of the nerve, the arachnoid becomes much thickened and infiltrated by the metastatic tumor cells, which partially invade the substance of the optic nerve (Luxol fast blue stain, ×2).

cally, the globes were unremarkable except for a small metastatic focus in the choroid of the right eye (Fig. 3). Specifically, the retinal photoreceptors were normal. The proximal optic nerves, however, showed marked plaque-like infiltration of the subarachnoid space by the metastatic tumor cells, with focal invasion into about 10% of the diameter of the nerve itself (Figs. 4-6). The axons in the nerve appeared normal, with minimal alteration of the myelin. Involvement of the optic nerve meninges was least at the globe and increased in severity more proximally toward the chiasm.

Discussion

Diffuse meningeal involvement with tumor was recognized in the 1800s, and its metastatic nature was appreciated in the early 1900s.[1-5] In 1901, Siefert[2,3] originated the term "meningeal carcinomatosis." The diagnosis is suggested by signs and symptoms of headache, dementia, meningeal irritation, and involvement of multiple cranial nerve or of spinal nerve roots with extremity or back pain.[1-10] Evidence for the condition in the cerebrospinal fluid includes reduced glucose concentration, increased protein concentration, and microscopic identification of malignant cells.[2-7,9-11] Impressive in our patient was the variation in the makeup of the spinal fluid, underscoring that in



Fig. 5 (Appen and associates). Higher power view of the right optic nerve shows the invasion into the periphery of the nerve by the tumor (hematoxylin and eosin, ×8).



Fig. 6 (Appen and associates). High-power view of the cells comprising the optic nerve infiltrate shows the identical appearance of the cells in the primary lung adenocarcinoma. Note abortive attempts at acinus formation (arrows) (hematoxylin and eosin, ×25).

some patients with meningeal carcinomatosis, multiple specimens of fluid are required to identify the malignant cells. The lack, as in our case, of a known primary malignancy does not preclude this diagnosis, as meningeal carcinomatosis was the first sign of the underlying malignancy in 50% and in 75% of two series of cases.[5,10] In selected patients, meningeal biopsy can be successful in establishing the diagnosis.[10]

As did our patient, persons with meningeal carcinomatosis frequently have communicating hydrocephalus,[1–6] presumably caused by the circulating malignant cells blocking the absorption of the cerebrospinal fluid by the arachnoid villi. The marked fluctuations of our patient's level of consciousness and alertness may have been somewhat related to decompressing lumbar punctures, but the significant metastasis to the choroid plexus of the third ventricle raises the possibility of a ball-valve effect that might intermittently aggravate the tendency to ventricular obstruction and dilation. A significant lesson is that a variable, waxing and waning clinical course does not exclude the possibility of a neoplastic etiology.[10]

Fischer-Williams, Bosanquet, and Daniel,[1] in 1955 and Katz, Valsamis, and Jampel[3] indicated that 30 to 40% of patients with meningeal carcinomatosis had associated loss of vision. However, two recent reports[5,6] suggest involvement of the second cranial nerve in only about 15% of patients with the condition. Histopathologic examination of cases of meningeal carcinomatosis with blindness has generally shown marked cuffing of the subarachnoid space of the optic nerve sheath by sheets of the metastatic cells,[1,3,4,7,8,12] and with rare exceptions, little actual invasion of the nerves themselves.[4,8,12] The precise mechanism for the impaired function of the optic nerve has not been clarified. Some have suggested that vascular perfusion of the nerve is hindered by the cuff of malignant cells,[7] whereas others suggested a humoral toxin.[1] Actual invasion of the nerve would clearly interrupt optic nerve transmission. Altrocchi, Reinhardt, and Eckman[4] have stressed that the entire optic nerve must be examined before one can conclude that invasion of the nerves has not occurred. In view of the remarkably normal appearance of the axons of the optic nerves of our patient, we propose that the loss of vision was secondary to a retinal photoreceptor degeneration as a remote effect of cancer, as reported by Sawyer and associates[13] in 1976. Although electroretinography was not performed in our patient, the abrupt onset of the blindness and, more importantly, the lack of histopathologic abnormalities of the photoreceptors would seem to exclude that possibility.

In our patient, we saw evidence of invasion into the nerve proximally, but the entire width of the nerve was not violated, and we are reluctant to attribute the blindness to this degree of invasion. The cuffing of the pia and arachnoid was impressive, and we suspect that arterial perfusion may well have been impaired.

The lack of extensive demyelination, however, suggests that there was not marked ischemia of the nerve. A dysfunction of axoplasmic flow in the optic nerve might play a role in this disorder. However, the precise mechanism for the loss of function of the optic nerve in meningeal carcinomatosis remains uncertain. The visual deficit in this setting may be reversed by remarkably low-dose irradiation to the head (William Hoyt, M.D., unpublished data, Feb. 18, 1977), and Olson, Chernik, and Posner[6] have reported encouraging results of combining irradiation with intrathecal chemotherapy. Such therapy may be of great psychological benefit to a patient with widespread metastatic disease who may be rendered bedridden by his other symptoms. The ophthalmologist or internist must consider the possibility of this condition when encountering a patient who has experienced bilateral visual loss.

Summary

A 53-year-old man had bilateral blindness secondary to meningeal carcinomatosis from pulmonary adenocarcinoma. Histopathologic examination of the visual system showed extensive infiltration of the arachnoid of the proximal optic nerves and chiasm, with minimal invasion of the optic nerves themselves. The visual pathways within the cerebral cortex were not affected.

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SUPRANUCLEAR OCULOMOTOR PALSY AND EXOTROPIA AFTER TETANUS

ALBERT W. BIGLAN, M.D., FORREST D. ELLIS, M.D., AND THOMAS A. WADE, M.D.

Indianapolis, Indiana

Tetanus is a neuromuscular disease that results from an infection with the anaerobic spore-forming bacteria, *Clostridium tetani.* Symptoms may be local or systemic, characterized by uncontrolled spasms of voluntary muscles, and they follow the production, transport, and fixation of the exotoxin, tetanospasmin, on the cell membranes of striated muscle and in the central nervous system. Complete recovery from the acute episode of this condition is the rule.

The paradoxical development of a cranial nerve palsy in patients with tetany is referred to as cephalic tetanus and was first described by Rose[1] in 1869. Unlike generalized tetanus, which characteristically resolves completely, cephalic tetanus may, in rare cases, leave a residual weakness of the affected nerve. Only one case of supranuclear palsy following tetanus has been described.[2] We describe herein a patient with generalized tetanus, transient supranuclear oculomotor palsy, and residual exotropia.

CASE REPORT

On Sept. 1, 1975, an 11-year-old boy was admitted to James Whitcomb Riley Hospital for Children with trismus, dizziness, and headaches. Seven days before admission, the patient had punctured his right foot with a "rusty nail." Local wound care, oral penicillin, and a diphtheria, pertussis, tetanus, booster were administered. Although a history of prior tetanus immunization was obtained, subsequent investigation showed this information to be incorrect.

On admission, the patient was afebrile. Increased muscle tone was apparent. Ophthalmic examination by the admitting physician was described as normal.

Admitting laboratory data included a hemoglobin count of 13.6 g/100 ml and a white blood cell count of 12,800/mm^3. The urinalysis, electrolytes, and chemistry screen and cerebral spinal fluid examination were normal. Cultures obtained from the wound were sterile. Intravenous penicillin was started, and the patient received 500 units of human tetanus immune globulin.

Twenty-four hours after admission, the patient developed clinical signs of tetanus with a temperature increase to 40° C, opisthotonic posturing, and increased muscle tone without hyperreflexia. Respiratory arrest occurred, which was treated by tracheostomy, paralysis with metocurine iodide, diazepam, and mechanical respiratory assistance. Although mannitol and dexamethasone were administered because of suspected increased intracranial pressure, the presence of papilledema was never proven.

During his clinical paralysis, the patient demonstrated external ophthalmoplegia refractory to caloric stimulation and Doll's head maneuver. The pupils were miotic and reacted to light. The patient gradually improved, and diazepam and metocurine iodide were no longer required to control his muscle spasms. The patient complained of diplopia for the first time. Both eyes were divergent at rest, and he was unable to adduct or elevate either eye. Down gaze was unimpaired. The pupils were equal and blepharoptosis was not present. The Bell phenomenon was demonstrable. The diagnostic impression was that a supranuclear oculomotor palsy secondary to tetanus existed.

On the 43rd hospital day, he was discharged with some improvement in his ability to elevate and to adduct his eyes. Diplopia and exotropia persisted. No other neuromuscular sequelae remained.

One year later full ocular rotations were present, but an exotropia of 45 prism diopters at distance and near persisted. The patient was readmitted, and extraocular muscle surgery consisting of recession of the right lateral rectus and resection of the right medial rectus muscles was performed. General physical examination at this time revealed no residual sequelae of the tetanus.

Six weeks after strabismus surgery, visual acuity was 6/4.5 (20/15) bilaterally and the pupils were 5 mm with normal reactions to light and accomodation. No deviation was present on alternate cover test at distance, and four diopters of exophoria were present at near. Amblyoscopic measurements demonstrated no ocular deviation. The patient was able to diverge 8 prism diopters and converge 15 prism diopters. He had stereopsis of 40 seconds of arc by the Titmus test. The patient was able to adduct both eyes fully. Horizontal and vertical saccadic velocities were equal and normal. The patient was able to accommodate on a target 8 cm from the eyes.

From the Indiana University School of Medicine, Department of Ophthalmology, Indianapolis, Indiana.

Reprint requests to Albert W. Biglan, M.D., 3518 Fifth Ave., Pittsburgh, PA 15213.

Discussion

The incidence of tetanus is decreasing in the United States. In 1976 only 67 cases were reported in this country.[3,4] Mortality remains high, however, and varied in recent series from 15% to 46%.[5,6] The development of cephalic tetanus has no adverse effect on mortality statistics.

The definition of cephalic tetanus has undergone considerable evolution since its initial recognition by Rose.[1] Several authors[7–11] have refined or modified the original criteria for the definition of cephalic tetanus. Dysfunction at the nuclear level of one or more of the cranial nerves has been suggested as the site of the palsy, but recently Saltissi[2] and his associates described a patient with tetanus and a supranuclear gaze palsy.

Our case and that described by Saltissi suggest that the definition of cephalic tetanus should be further modified. It should be considered as a variant of tetanus associated with either a nuclear or supranuclear cranial nerve palsy.

The incidence of a cephalic tetanus is rare, and Vakil[12] noted only a 1.1% incidence after reviewing 1,843 patients with tetanus. Brown[7] later reviewed 94 patients who had cephalic tetanus and found only 12 patients with oculomotor dysfunction. Wetzel[13] reviewed 30 patients with tetanus following injury to the eye and found three patients with a third nerve palsy, all of whom had blepharoptosis, but only two of whom had pupillary involvement. A summary of preceding studies shows that when cranial nerves are involved, the seventh, sixth, third, and fourth are involved with decreasing order of frequency, and there is usually a favorable prognosis for recovery.

The patient we described had Grade 5 tetanus as classified by Patel and Mehta[14] and results of an eye examination on admission were normal. After three weeks of therapy for generalized tetanus, he had a persistent divergent strabismus and a supranuclear gaze palsy. Early attempts at investigating the cause of this ophthalmoplegia were unsuccessful because of the intermittent use of metocurine. Following his recovery from generalized muscle spasms after metocurine was discontinued, the continued presence of an upward gaze palsy with an intact Bell's phenomenon and the absence of blepharoptosis and significant pupillary findings suggested a persistent defect at the supranuclear level.

Miotic pupils seen in our patient during the acute phase of his illness may occur with tetanus.[15] In clinically manifest tetanus, the pupils are often miotic, but they also may be dilated and fixed if signs of third nerve palsy coexist. Alternations in sympathetic tone and autonomic dysfunction[16] have affected the cardiovascular system in other patients with tetanus.

Although blepharoptosis was not present in our case, it frequently occurs in other patients with cephalic tetanus. After an unsuccessful search for a sympathetic cause of the blepharoptosis in his patients, Vakil[12] concluded that blepharoptosis was caused by involvement of the third nerve nucleus.

Cranial nerve palsies in cephalic tetanus are not related to the site of the injury, and these palsies may be overlooked because of the condition of the patient. There is usually a delay between the onset of generalized tetanus and the development of the cranial nerve palsy, but cases have been reported in which the cranial nerve palsy was the first sign or developed before the tetanus.[8] Although head trauma is frequently associated with cephalic tetanus, it is not a prerequisite, and our case clearly excludes head trauma as a cause of the palsy.

The anatomic location of the cranial nerve dysfunction remains unclear. Indirect evidence from electromyographic

studies has implicated the cranial nerve nuclei as the site of the cranial nerve palsy. This is supported by Bagratuni[5] and Baker[17] who reviewed the work of Eishner and described 12 cases in which degenerative changes had occurred in the motor nuclei. Murphy[18] confirmed this finding in a patient who died from tetanus and had histopathologic changes in the cytoplasm of nuclear cells. Although these reports are convincing, Park[11] could not confirm these findings in autopsies of other cases.

The mode of transmission of the toxin to the central nervous system remains controversial.[19] There is indirect evidence for movement of the toxin within the nerve bundle, but not within the axon. Evidence also indicates that the toxin reaches the central nervous system by way of the systemic circulation.

Our patient recovered from his palsy and had residual exotropia. Normal saccadic velocities, accommodation, and convergence returned during follow-up examinations. Signs of aberrant third nerve regeneration were absent. The possibility of a decompensated pre-existing exotropia was investigated. No history of previous ocular abnormalities was obtainable, and old photographs did not show any strabismus. The presence of stereopsis and fusional amplitudes after surgical alignment also supports a recent onset of the strabismus.

The surgical correction of the exotropia was undertaken after a one-year waiting period and was managed as any other strabismus. We attribute the excellent functional result obtained to the patient's pre-existing sensory development.

Summary

An 11-year-old boy developed generalized tetanus complicated by a supranuclear gaze palsy and exotropia. This case led us to include supranuclear palsy in an expanded definition of cephalic tetanus.

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AMAUROSIS AND BLOOD LOSS

KRISTINE M. KLEWIN, M.D., RICHARD E. APPEN, M.D., AND PAUL L. KAUFMAN, M.D.

Madison, Wisconsin

Centuries ago, it was recognized that visual loss can result from severe blood loss.[1] Although recent ophthalmologic studies have discussed this association, there is only one report of a patient with unilateral total blindness[2] and none of a patient with bilateral total blindness. In nonophthalmologic studies, there are three descriptions of patients with the latter complication of hemorrhage.[3–5] We describe herein a patient who sustained permanent bilateral blindness as a complication of gastrointestinal hemorrhage.

CASE REPORT

A 57-year-old man who had a history of alcohol abuse for many years awoke three days before admission to the hospital with bilaterally blurred vision. His symptoms gradually worsened so that on admission to the hospital, he had light perception only. He had no associated eye pain, headache, scalp tenderness, fever, chills, meningismus, syncope, limb weakness, diplopia, dysarthria, or dysphagia.

Five years before admission, the patient had undergone partial gastrectomy for a perforated peptic ulcer. During the past year, his weight had decreased by 40 pounds. For several weeks, while taking six to eight aspirin tablets daily for leg pain, he had experienced intermittent nausea, vomiting, and progressively increasing epigastric pain. For five days he had had melena and postural hypotension.

On admission on Oct. 23, 1975, the patient was emaciated (106 pounds) but alert and cooperative. He was afebrile. Blood pressure was 110/70 supine and decreased to 95/60 in a seated position; pulse was 92 beats per minute. Cardiac examination was unremarkable. Pulses were absent below the femoral arteries bilaterally, and the right leg was cooler than the left.

Ophthalmic examination revealed visual acuity of light perception only bilaterally. The eyes appeared normal externally. Ocular motility was normal. The pupils were 5 mm and minimally reactive to light. The anterior segments were normal. Intraocular pressures were 14 mm Hg bilaterally. The optic disks were pale, and one diopter elevated. The retinal arterioles were narrowed, and the veins tortuous and congested. No retinal emboli were visible (Fig. 1). Ophthalmodynamometric readings (Baillart) were: R.E.: 60/30; L.E.: 50/20. There were no ocular bruits. The superficial temporal arteries were nontender and symmetrically pulsatile.

Laboratory investigation revealed: hematocrit, 23%; hemoglobin concentration, 7.3 g/100 ml; erythrocyte sedimentation rate, 55 mm/hr(Wintrobe method); white blood cell count, 12,000/mm^3 with a normal differential cell count. Blood chemistry measurement showed increased hepatic indices (total bilrubin, 2.0 mg/100 ml; lactic acid dehydrogenase, 414 IU/liter; glutamic oxaloacetic transaminase, 59 IU/liter; alkaline phosphatase, 150 IU/liter, but normal values for serum concentrations of calcium, glucose, blood urea nitrogen, uric acid, protein, creatinine, and electrolytes. Stool examination yielded a positive guaiac test for blood. Cerebrospinal fluid revealed three mononuclear white blood cells per milliliter and normal glucose and protein concentrations. Skull roentgenogram showed considerable calcification of the intracranial vessels, but no other definite abnormalities. Computed axial tomographic scan showed moderate cortical atrophy, but no abnormalities in the region of the optic chiasm. Right superficial temporal artery biopsy on Oct. 24, 1975, showed evidence of medial fibrosis, but no inflammation. Upper gastrointestinal endoscopy showed two 6 × 8-mm gastric ulcers and a 2 × 3-cm duodenal ulcer, although upper gastrointestinal x-ray films using barium sulfate showed only deformity of the distal antrum and duodenum. Femoral arteriography showed severe atheromatous disease bilaterally. The right common femoral artery was occluded. The left hypogastric artery and left superficial femoral artery were occluded, but there was good collateral flow to the left leg.

Initial treatment consisted of blood transfusions, and, because of the possibility of giant cell arteritis, an intensive one-week course of systemic cortiocosteroids. Right femoral thromboendarterectomy was carried out on the day after admission, with restoration of the circulation to the right leg. Microscopic examination of the specimen from that procedure showed an organized thrombus about a calcified plaque, without evidence of arteritis. Medical measures for the peptic ulcers were started, and follow-up endoscopy showed healing of the ulcers three weeks later.

The patient lost light perception one day after admission; thereafter visual function remained nil, and the pupils remained unresponsive to light. Within two weeks after admission, the disk swelling

From the Department of Ophthalmology University of Wisconsin Center for Health Sciences, Madison, Wisconsin.

Reprint requests to Richard E. Appen, M.D., Department of Ophthalmology, University of Wisconsin Hospitals, 1300 University Ave., Madison, WI 53706.

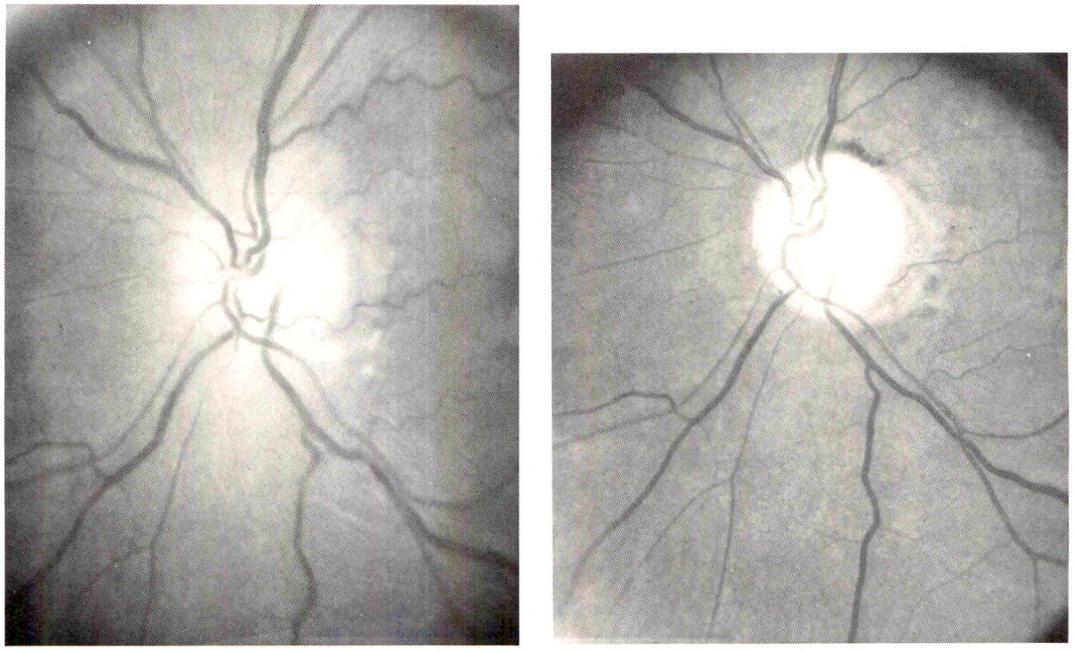


Figure (Klewin, Appen, and Kaufman). Left, Left eye three days after patient's admission to hospital. Note pallor and swelling of optic disk. Right optic disk (not shown) had similar appearance. Right, Left eye seven months later showing marked optic atrophy and narrowed retinal vessels.

had regressed, and the disks became whiter. Seven months later, although otherwise in good health, the patient remained totally blind bilaterally. Both disks were white, with shallow cups and a cup:disk ratio of 0.7, and the retinal arterioles were narrowed (Figure, right).

The patient died on Sept. 25, 1976. Autopsy disclosed diffuse severe atherosclerotic vascular disease, with recent thrombosis of the inferior mesenteric artery and resultant gangrene of the colon. The brain showed no gross or microscopic abnormality of the visual pathways, but the optic nerves were atrophic. The eyes were not examined.

Discussion

Hippocrates in the fifth century BC is credited with the earliest known description of amaurosis secondary to severe blood loss.[1] In 1902 Singer[6] reported two cases that he had personally seen and reviewed an additional 172 cases from previous reports, for a total series of 174 cases. In 1950, Hollenhorst and Wagner[1] described five patients who were examined months after they experienced partial loss of vision after hemorrhage and reviewed previous reports extensively. In 1971, Lazaro and associates[3] discussed a patient whose clinical course closely resembled that of our patient.

Visual loss after severe hemorrhage generally occurs in debilitated persons 40 to 60 years of age who sustain repeated episodes of bleeding. It is rare among healthy persons who have marked hemorrhage from acute trauma, such as soldiers with war injuries.[1] In Singer's[6] series, the gastrointestinal tract was the site of bleeding in 40% (76/189) of all cases (76% in men) and the uterus in 33% (62/189) of all cases. Typically, the visual impairment occurs abruptly after a variable interval from the time of the most severe hemorrhaging. Of Singer's[6] series, the loss of vision occurred at about the time of hemorrhage in 20% (24/120), within the next 48 hours in 33% (40/120), and

three to ten days later in 39% (47/120) of the patients. As in our patient, and in most cases described in recent years,[1-5,7,8] the location of the damage to the visual pathways is generally the distal optic nerve, accounting for the sluggishly reactive pupils and the ophthalmoscopic appearance of ischemic optic neuropathy[9-12] in the acute phase, followed by optic atrophy several weeks later. Occasionally, ischemic cerebral damage affecting the optic radiations can produce the visual impairment, as evidenced by Grout's[13] finding of homonymous hemianopia in 10% of patients with posthemorrhagic visual loss.

Both eyes are generally involved, as in 88% (170/194) of Singer's series.[6] The severity of the insult is variable. Drance, Morgan, and Sweeney[7] and Drance[8] described patients with hemodynamic crises who developed glaucoma-like cupping of the optic disk and nerve fiber bundle visual field defects, but in whom central vision remained good and progression did not occur. They termed this shock-induced optic neuropathy and distinguished this entity from other forms of low-tension glaucoma that do show progressive deterioration. However, in our patient, the loss of vision was complete, and the optic nerves developed total atrophy without severe glaucoma-like cupping, resembling the appearance of ischemic optic neuropathy.[9-12] Multiple host-related factors probably determine the degree of damage that an individual optic nerve sustains in response to the hemodynamic crisis. The prognosis for recovery is difficult to predict for a given patient. Unger[14] found that the visual deficit was permanent in 55% (101/186), improved in 34%, and returned to normal in 11%, whereas Singer[6] reported that 46% (70/151) of the patients showed no improvement.

The precise pathogenesis of the visual impairment is uncertain, although the loss of blood seems to be the initiating event and results in an ischemic insult to the distal optic nerves. Any hypothesis must explain the predilection for debilitated persons, the delay between the hemorrhage and the onset of the visual loss, and the rarity of the condition in young, healthy persons following massive hemorrhage after trauma. Pertinent variables may include the basic health of the optic nerves, the state of blood vessels supplying the nerves, and the constituents of the blood (hemoglobin, proteins, and possibly metabolites whose significance has not yet been appreciated) perfusing them. Perhaps in the future, better understanding of this disorder will help clarify the equally enigmatic pathogenesis of the more common ischemic optic neuropathy not associated with severe blood loss.

The ophthalmologist must recognize the association of visual loss with severe blood loss elsewhere to aid in correct diagnosis and to facilitate prompt replacement of blood and appropriate management of the source of hemorrhage.

Summary

A 57-year-old alcoholic man sustained permanent bilateral blindness and optic atrophy as a complication of hemorrhage from peptic ulcer disease. Posthemorrhagic visual loss occurs in middle-aged, debilitated persons a short time after repeated episodes of hemorrhage from any site.

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OPHTHALMIC MINIATURE

The agonized search for an answer gave rise to such theories as transmission by sight. "People fall ill," wrote Guy de Chauliac not only by remaining with the sick but, "even by looking at them." Three hundred years later Joshua Barnes, the 17th century biographer of Edward III, could write that the power of infection had entered into beams of light and "darted death from the eyes."

Barbara W. Tuchman,
A Distant Mirror—The Calamitous 14th Century
New York, Alfred Knopf, 1978

RETINAL GANGLION CELL DEGENERATION IN EXPERIMENTAL OPTIC ATROPHY

RONALD L. RADIUS, M.D., AND DOUGLAS R. ANDERSON, M.D.

Miami, Florida

The onset of descending optic atrophy following various lesions to the optic nerve may reflect the distance between the ganglion cell bodies and the axonal lesion.[1] For example, the degeneration following transsection of the optic nerve at the globe might occur more rapidly than the degeneration resulting from a more posterior lesion involving the optic tract or the chiasm.

Recent observations, however, have suggested that the time of occurrence of ganglion cell degeneration and axon atrophy may be independent of the position of the insult. In primates, optic atrophy has been noted within four to six weeks after an insult with lesions involving either the orbital optic nerve or the optic tract.[2–6]

We undertook to determine whether intraretinal interruption of the nerve fibers would produce degeneration of the ganglion cells more rapidly than lesions involving the more posterior portions of the optic pathways. Retinal nerve fiber layer injury was accomplished by circumpapillary retinal photocoagulation in monkey eyes. The rate of ganglion cell degeneration was quantified by histologic ganglion cell counts at various intervals after photocoagulation.

From the William L. McKnight Vision Research Center, Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami School of Medicine, Miami, Florida. This investigation was supported in part by Public Health Service Research Grant EY-00031 (Dr. Anderson) and Training Grant EY-07021 (Dr. Radius) awarded by the National Eye Institute, Bethesda, Maryland. Dr. Anderson is a William and Mary Greve International Scholar, awarded by Research to Prevent Blindness, Inc.

Reprint requests to Douglas R. Anderson, M.D., Bascom Palmer Eye Institute, P.O. Box 520009, Miami, FL 33152.

MATERIAL AND METHODS

Xenon arc photocoagulation was performed in eyes of owl monkeys *(Aotus trivirgatus)* in a circumpapillary, superior arcuate fashion (Fig. 1). Each animal was observed by ophthalmoscopy and its fundi photographed. Eye tissues were examined by histopathology at various intervals: two (two eyes), three (five eyes), four (five eyes), six (four eyes), and ten weeks (four eyes) after photocoagulation. Five untreated eyes were included as normal specimens in subsequent analyses. To obtain the tissue, anesthetized animals were either perfused by a retrograde intra-arterial route with buffered 4% paraformaldehyde fixative or given a fatal dose of pentobarbital intravenously. The eyes were enucleated and immersed in paraformaldehyde fixative.

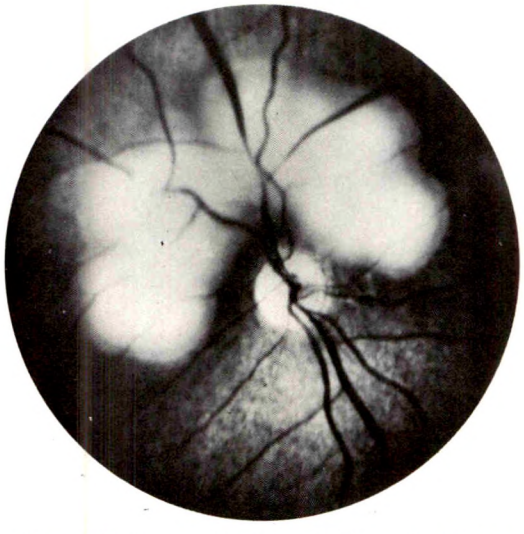


Fig. 1 (Radius and Anderson). Example of acute retinal photocoagulation in experimental monkey eyes with burns patterned to effect superior hemipapillary atrophy. Sections were oriented after fixation to insure examination of areas whose axonal processes were included in retinal photocoagulation.

To assure proper orientation of the treated hemiretina during sectioning, all the eyes were opened horizontally just below the optic nerve head. After the superior cap was removed, the eyes were embedded in paraffin and sectioned through the nerve head in a horizontal plane. Sections 8 μ thick were taken at every 0.1 mm. To be sure that the counted area was in the area affected by the photocoagulation, only sections that showed burns on both the nasal and temporal sides of the disk and included only superior retina were used for ganglion cell counts.

Ganglion cell counts were performed under oil immersion (magnification 125 ×). For counting, the retina temporal to the optic nerve head was subdivided into three 4-mm regions beginning 1.5 mm from the disk margin, thus excluding the photocoagulated retina and the immediately adjacent area. The retina nasal to the disk was similarly divided into three 3-mm regions. The cell counts from each region on each of five to seven slides were averaged for every treated eye. The average cell counts for each retinal area from each of several eyes enucleated at identical times after photocoagulation were averaged. The data are presented as the mean cell count ± one standard error of the mean for the eyes treated at specific intervals before enucleation.

Results

Optic disk pallor developed in some animals as early as two weeks after treatment. By six weeks, all animals had demonstrated optic disk pallor, confirming that the photocoagulation had interrupted the nerve fiber layer and produced ascending degeneration of axons central from the retinal burn. Additionally, at six weeks, the retinal nerve fiber layer degeneration could be seen ophthalmoscopically peripheral to the retinal burn. Histo-



Fig. 2 (Radius and Anderson). Photomicrograph of retinal photocoagulation lesion six weeks after therapy. All retinal layers are involved in chorioretinal scarring (hematoxylin and eosin. ×75).

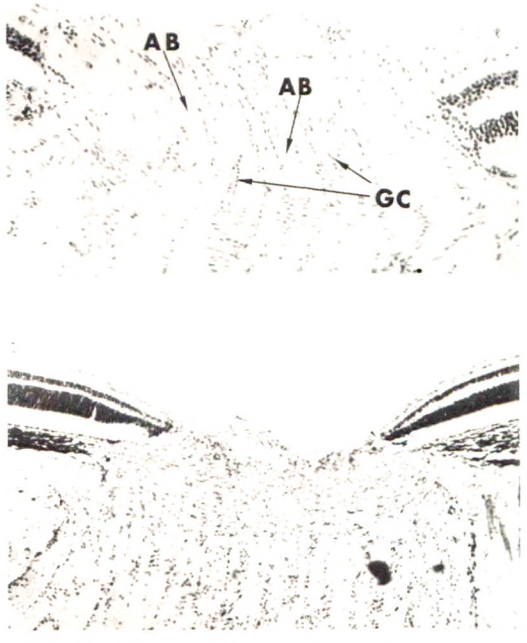


Fig. 3 (Radius and Anderson). Top, Normal optic nerve head demonstrates glial cell columns (GC) and intact axonal bundles (AB). Bottom, Conversely, eyes examined six weeks after retinal photocoagulation demonstrated ascending optic atrophy. Disorganized glial architecture and increased cellularity are consistent with optic atrophy following interruption of retinal axons by photocoagulation (hematoxylin and eosin, ×50).

pathologically, the chorioretinal scarring in areas of retinal photocoagulation involved all retinal layers (Fig. 2). Furthermore, there was ascending optic atrophy in all specimens examined (Fig. 3).

The retinal ganglion cell counts at various intervals after photocoagulation (Table, Figs. 4 and 5) reveal the onset and progression of the degeneration of the ganglion cells whose axons traverse the retinal burns. In the retina temporal to the disk, the ganglion cell count was the same in the untreated eyes as in the eyes enucleated two and three weeks after retinal photocoagulation (Fig. 6). At four weeks, there was a statistically significant ($P<.05$, Student t-test) reduction in the number of ganglion cells in the treated eyes compared to the untreated eyes, and to the eyes treated two and three weeks before the killing of the animals (Fig. 6). A further decrease in the ganglion cell count ($P<.05$) was apparent when the eyes enucleated six weeks after photocoagulation were compared with the eyes examined four weeks after photocoagulation (Fig. 6). There was no apparent additional decrease in cell population at ten weeks.

The individual areas temporal to the disk, each increasingly distant from the optic nerve head, showed a similar pattern when each was analyzed separately (Table, Fig. 4). Area 1 included the perimacular retina with ganglion cells closest to the experimental lesion. Here, a statis-

TABLE

RETINAL GANGLION CELL COUNTS*

No. of Animals Studied	Time Interval† (wks)	Pooled Areas	Area 1	Area 2	Area 3
			Temporal Retina		
2	2	392 ± 25	148 ± 31	152 ± 27	92 ± 16
5	3	424 ± 11	111 ± 3‡	170 ± 11	114 ± 3
5	4	300 ± 5‡	104 ± 14‡	129 ± 2‡	66 ± 8
4	6	205 ± 4‡	66 ± 5‡	79 ± 2‡	60 ± 6
4	10	208 ± 8‡	51 ± 12‡	89 ± 4‡	67 ± 6
Control					
5		466 ± 22	190 ± 14	188 ± 20	90 ± 11
			Nasal Retina		
2	2	244 ± 29	92 ± 8	70 ± 6	64 ± 9
5	3	176 ± 22	60 ± 9	55 ± 8	42 ± 6
5	4	205 ± 16	52 ± 2‡	55 ± 4	50 ± 6
4	6	124 ± 22‡	46 ± 9	38 ± 7‡	31 ± 7
4	10	156 ± 6‡	49 ± 2‡	44 ± 4	36 ± 2‡
Control					
5		250 ± 30	105 ± 16	68 ± 8	53 ± 5

*Retinal areas 1, 2, and 3 are each increasingly distant from the disk margin in eyes enucleated at various intervals after retinal peripapillary photocoagulation. Pooled counts for three temporal and three nasal retinal areas are included. Data are presented as mean ganglion cell count ± one standard error of the mean for each of several time intervals.

†Time interval in weeks between retinal photocoagulation and enucleation.

‡Mean ganglion cell count for specific time interval and retinal area showed a statistically significant (Student t-test) difference from that observed in five untreated eyes ($P<.05$).

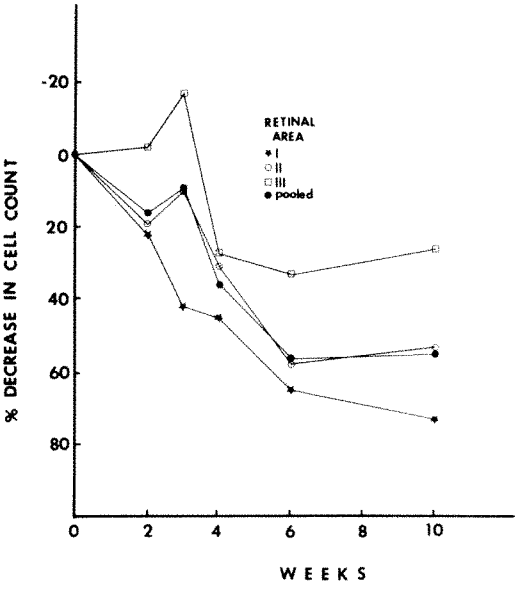


Fig. 4 (Radius and Anderson). Percentage reduction in ganglion cell count for each of three temporal retinal areas 1, 2, and 3 as well as pooled data recorded at each of several time intervals studied. Ganglion cell degeneration was apparent by three to four weeks after retinal ablation and this atrophy appeared to plateau between six and ten weeks.

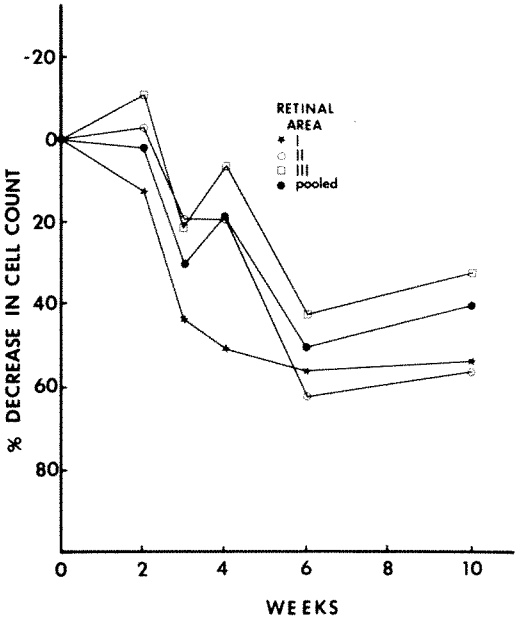


Fig. 5 (Radius and Anderson). Percentage reduction in mean ganglion cell count for each of three nasal retinal areas 1, 2, and 3 as well as pooled data recorded at each of several time intervals studied. Ganglion cell degeneration was apparent by three to four weeks after retinal ablation and seemed to plateau between six and ten weeks.

tically significant ($P<.05$) decrease in the cell population occurred as early as three weeks after photocoagulation. Areas 2 and 3 showed decreases in the number of ganglion cells at four weeks, although the reduction in area 3 was not established statistically ($P<.1$). The reduction in the ganglion cell counts appeared to plateau between six and ten weeks (Fig. 4).

Although the results from the analyses of the nasal retinal areas were more variable, the patterns were similar (Fig. 5). Pooled data from the three nasal retinal areas demonstrated a reduction in the number of ganglion cells as early as three weeks after retinal ablation. However, because of a greater data variability, this decrease did not reach statistical significance until six weeks after photocoagulation ($P<.05$). When the individual areas were considered separately, a statistically significant ($P<.05$) reduction in the cell count was first documented at four, six, and ten weeks, respectively in areas 1, 2, and 3.

Even as late as ten weeks after retinal photocoagulation, some ganglion cells were still evident in the examined retinas. Perhaps some axons escaped injury even though the histopathologic examination of both the acute and the chronic lesions suggests that the photocoagulation was adequate to have interrupted all the axons. Perhaps some portion of these cells remaining in the ganglion cell layer are either glia or interneurons that do not send axons toward the optic nerve head. A third possibility is that axons from some ganglion cells included in the examined retina may arc around the area of retinal photocoagulation, thus escaping injury. However, careful orientation of the specimens during embedding and sectioning should have minimized the number of such cells.

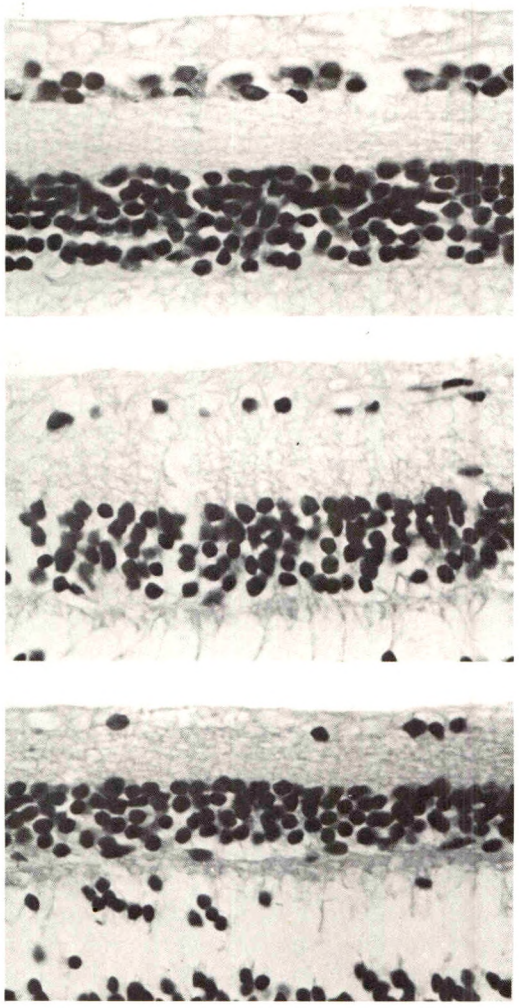


Fig. 6 (Radius and Anderson). Photomicrograph of retinal sections from eyes studied before and four and six weeks after retinal photocoagulation. Top, Normal ganglion cell layer shows double row of neuronal soma. No significant difference in number of ganglion cells was apparent in eyes from animals killed two and three weeks after photocoagulation when compared to those untreated specimens. Center, Retinas examined four weeks after retinal photocoagulation showed early reduction in ganglion cell count. Bottom, Six weeks after retinal treatment, evidence of extensive descending atrophy was apparent with marked reduction in ganglion cell count. No further decrease in cell population was seen at ten weeks (hematoxylin and eosin, ×200).

Discussion

In these experimental animals, both the ophthalmoscopic and histopathologic examinations confirm the interruption of the nerve fiber layer by the intense retinal photocoagulation. Of course, this thermal energy produces lesions that are different from transsection of the optic nerve. However, both represent a physical interruption of the axons, and with respect to study of ganglion cell degeneration, these two axonal injuries reasonably can be compared.

Disk pallor developed as early as two weeks after the retinal photocoagulation, which agrees with previous observations in squirrel monkeys that the axonal segment separated from the ganglion cell body degenerates promptly.[4] However, the ganglion cells and the proximal axonal segments survive longer.[4,5] In our study, the ganglion cells and nerve fiber layer had not changed perceptibly at two weeks after the photocoagulation. By three weeks, however, some specimens showed an early decrease in ganglion cell counts, especially in the perimacular areas (area 1). Four weeks after retinal photocoagulation, the ganglion cell population had decreased significantly; and by six weeks, this degeneration had apparently plateaued. Thus, the time of onset and the progression of the ganglion cell atrophy in these eyes is similar to that which follows transsection of the optic nerve in the posterior orbit of owl monkeys.[5] The timing of degeneration is evidently not affected by the distance of the ganglion cells from the injury.

Another approach to determining whether distance from the lesion influenced timing of ganglion cell death is to compare the individual retinal areas in this experiment. When comparing treated and untreated eyes, a statistically significant ($P<.05$) reduction in the number of ganglion cells appeared at later time intervals in the more peripheral retinal areas (Table). These small differences in the onset of atrophy between different retinal areas may suggest that the more peripheral ganglion cells degenerate at later time intervals. However, these dif-

ferences in onset of cell atrophy from one retinal area to another were small compared to the three- to six-week period over which cumulative cell atrophy occurred in each retinal area. A small delay in the onset of degeneration of the more peripheral ganglion cells could be concealed by this relatively long three-week interval. However, all retinal areas, as well as the pooled data, showed onset and progression of ganglion cell atrophy identical to that seen following optic nerve transsections located 2 to 3 cm more posteriorly. If these intraretinal distances were really significant, descending atrophy following posterior transsection should have shown a comparable delay in onset.

Factors other than the distance from the cell body to the insult are more likely to be important to the timing of the ganglion cell degeneration. For example, there may be biologic variability or specific differences in type or size of the various retinal ganglion cells, which may explain differences in the timing of the degeneration of the macular fibers compared to that of the more peripheral retinal cells.[5] Such variability is probably more significant with respect to the variation in cell atrophy seen in different retinal areas rather than varying distances from the axon insult.

The exact cellular mechanism of retrograde degeneration is not known, but current theory suggests that the cell body degeneration is initiated when the neuronal soma is separated from the appropriate end organ for longer than some specific length of time. Presumably, the cell body suffers the loss of some trophic substance coming from the axon terminals and transported retrograde to the cell nucleus.[7,8] Given the known rates of retrograde transport, the cell body should stop receiving this chemical messenger within a day.[5,9] If the cell atrophy occurred as soon as this chemical messenger stopped arriving, degeneration would begin within a matter of hours. The distance from ganglion cell to insult might determine whether this began as early as one hour or as late as four to six hours after injury. In reality, however, there must be some cumulative effect, with the atrophy becoming apparent only after a much longer time interval of several weeks. The distance from the cell body to the injury could presumably affect this period by only a matter of several hours and would be negligible, provided the latent period representing the cumulative effect is not dependent on the distance from the injury. Teleologically speaking, this delay is essential for nerves capable of regeneration to allow time to re-establish contact with the appropriate end organ. If degeneration began as soon as material ceased to arrive at the cell body, such regeneration would be impossible. Furthermore, if contact with the end organ is re-established before the latent period has ended, the renewed arrival of trophic substance at the cell body must be able to prevent the onset of the degenerative process.

Thus both theoretical and experimental considerations suggest that the timing of the atrophy of the cell body (and of the attached axon segment, which degenerates at the same time as the cell body[5]) is independent of the injury's location. Perhaps the clinical observations to the contrary reflect differences in the nature of the lesion characteristic of particular locations rather than the distance of the insult from the retinal ganglion cell. For example, instances that involve transsection of the optic nerve, characteristic of orbital lesions, will show nerve atrophy in three to six weeks. Other lesions, such as tumors of the chiasm, will slowly expand to compromise the individual axons at different times. In the first case, all

axons are affected simultaneously, with striking disk pallor developing within three to six weeks. In the latter instance, the individual axons are injured at various intervals and clinical pallor gradually ensues over a prolonged period of time, taking a longer time to achieve an advanced degree of atrophy. Although the timing of total disk atrophy may differ, the interval between injury and ganglion cell atrophy is identical for each individual axon.

Summary

By ophthalmoscopic and histopathologic examinations at various intervals after retinal injury, we studied progressive ganglion cell atrophy following retinal photocoagulation in 25 owl monkey eyes. A reduced ganglion cell population was apparent within three to four weeks after the photocoagulation and was maximal by six weeks.

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MELANOCYTIC TUMOR OF THE ANTERIOR UVEA

EDWIN B. DUNPHY, M.D., THADDEUS P. DRYJA, M.D., DANIEL M. ALBERT, M.D., AND TAYLOR R. SMITH, M.D.

Boston, Massachusetts

Iris melanomas are benign uveal tract melanomas.[1] When they are small and they do not threaten to involve the angle, these lesions are clinically followed and growth is documented. Sector iridectomy or iridocyclectomy is the usual treatment for a small lesion. However, large lesions having marked ciliary body invasion and tumors that recur after local excision are more lethal. In a retrospective study of the prognosis of iris melanomas treated initially with iridectomy, six patients had recurrence requiring enucleation and two of these patients died because of the tumor.[1] Melanomas arising in the ciliary body carry a poor prognosis, because such lesions may extend into the iris. When possible, cyclectomy or iridocyclectomy is advised.[2]

We report herein the clinical and pathologic findings in the case of a patient with a spindle melanoma involving, at the time of eventual enucleation, the iris and ciliary body. The tumor had grown progressively for 13 years before enucleation. The patient is alive and clinically free of metastases 32 years after enucleation. This is remarkable because the tumor was present in the ciliary body and had spread along ciliary vessels to the subconjunctival region. Dunphy[3,4] previously referred to this case and advocated conservative management of tumors.

CASE REPORT

In 1933, a 32-year-old woman had an iris melanoma in her left eye. The iris tumor extended from 6 to 8 o'clock, according to the only records available from that time. Theodore L. Terry, M.D., Walter B. Lancaster, M.D., and Edwin B. Goodall, M.D., of the Harvard Medical School and Massachusetts Eye and Ear Infirmary, recommended immediate enucleation. However, the patient refused enucleation and was lost to further follow-up until 1946; at this time she had a blind, painful, glaucomatous eye. A dark area was observed subconjunctivally a few millimeters from the corneoscleral limbus. Severe corneal edema was present and did not clear with topical glycerine treatment. She agreed to enucleation and on Nov. 5, 1946, the tumor was removed. The patient is still alive and well at age 77 years, and no clinical symptoms of metastasis are present.

RESULTS

A moderately pigmented spindle melanoma involved the iris and the anterior third of the ciliary body (Fig. 1). The tumor was evident in the anterior stroma of the iris. It was seen at the iris root on both sides of the sections studied, and therefore, the tumor involved a major portion of the circumference of the iris. The tumor filled the angle on both sides of the specimen and produced an anterior synechia on one side (Fig. 1), as well as an ectropion uveae also apparently induced by the tumor. Tumor cells were present in the sclera along anterior ciliary vessels

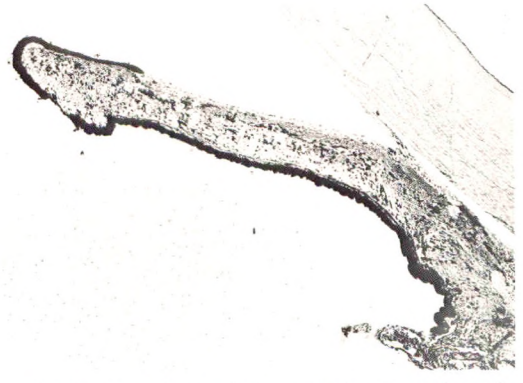


Fig. 1 (Dunphy and associates). Iris and angle structures showing tumor infiltration, ectropion uveae, and anterior synechia (×30).

From the Howe Laboratory of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

Reprint requests to Daniel M. Albert, M.D., Howe Laboratory of Ophthalmology, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114.

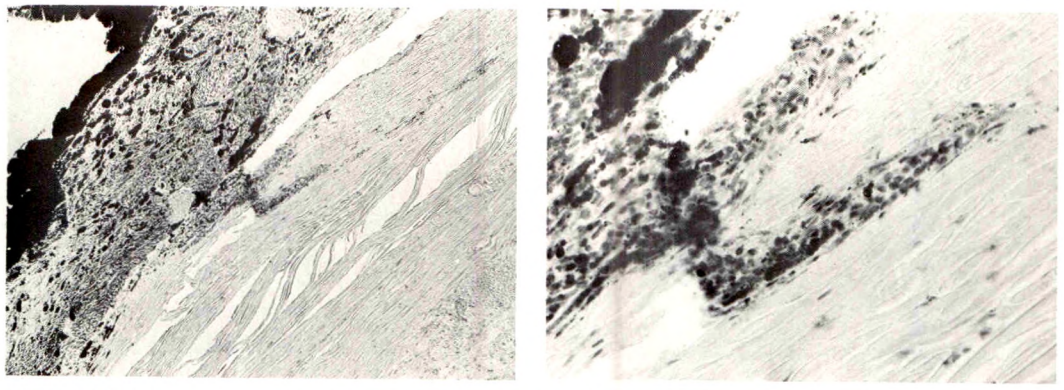


Fig. 2 (Dunphy and associates). Anterior ciliary body and sclera showing presence of tumor in emissary (left, ×75; right, ×300).

(Fig. 2), and near this area, foci of tumor cells were evident around subconjunctival vessels (Fig. 3). A small focus of tumor cells lay in the vitreous adjacent to the pars plana (Fig. 4, left).

Surrounding and within the tumor were many macrophages filled with brown pigment. Little observable inflammatory response to the tumor was noted. The tumor cells were of the spindle type with a deeply basophilic nucleus and rare nucleoli (Fig. 4, right). Few mitoses were evident. Occasional nests of cells suggestive of nevus structures were present in the iris and ciliary body.

The cornea was edematous; the anterior chamber was otherwise normal. The lens showed epithelial proliferation, bladder cell formation, marked globule formation, and liquefaction in the anterior and posterior lens cortex. The retina showed complete absence of ganglion cells. Severe optic cupping and optic nerve atrophy were evident.

Electron microscopy was performed on sections cut from the original celloidin

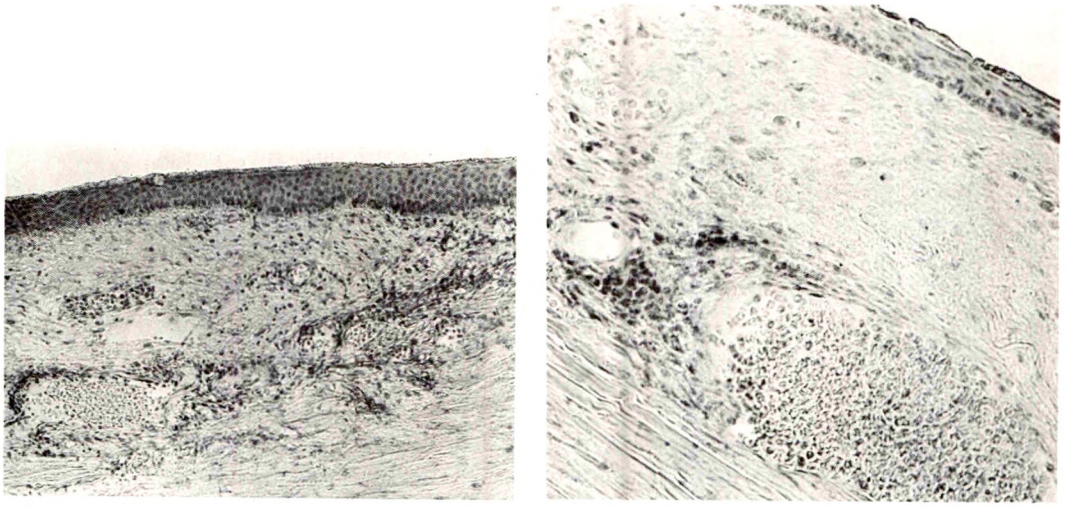


Fig. 3 (Dunphy and associates). Conjunctival blood vessels surrounded by tumor cells (left, ×85; right, ×200).

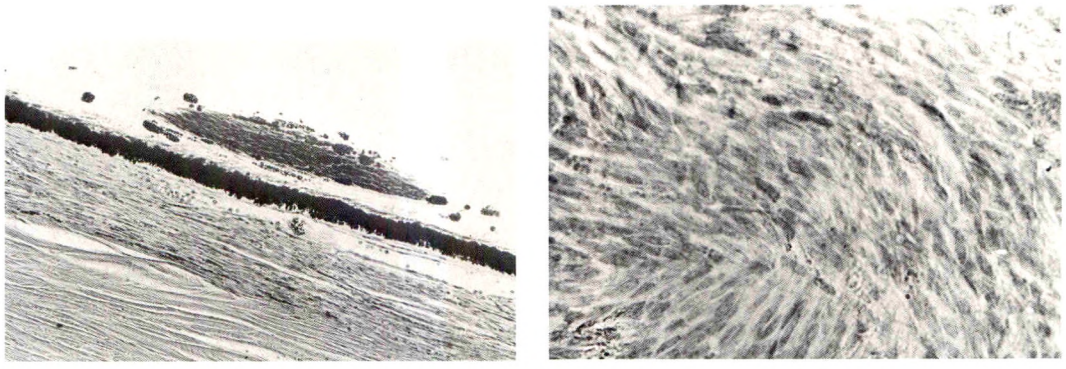


Fig. 4 (Dunphy and associates). Left, Metastatic collection of tumor cells underlying pars plana (×210). Right, Spindle cells in ciliary body (×335).

block. Cellular details were not well preserved, however, and little additional information was obtained.

Discussion

Iris melanomas often arise from preexisting nevi. In one study of iris melanomas treated with iridectomy, approximately 30% of the patients stated that a pigmented lesion had been noticed for more than five years before diagnosis.[1] In another study, 37% of the patients with iris melanomas had observed a pigmented spot on the iris since birth.[5] It is not correct to assume that these patients had a malignancy for many years before enucleation; more likely, the patients were describing a long-standing benign lesion that had only recently undergone malignant change. The case reported herein differs in that the size and appearance were sufficiently suggestive of a malignant tumor in 1933, 13 years before it was removed, to cause three ophthalmologists to suggest enucleation. Before enucleation, the tumor had locally invaded the iris and ciliary body, and was present along ciliary vessels and in the subconjunctival region. Blood vessels were surrounded with tumor both intraocularly and subconjunctivally. A focus of tumor extended into the vitreous overlying the pars plana.

It is not clear whether the presence of tumor in the ciliary body represents spread of iris melanoma into the ciliary body. The comparatively large bulk of tumor in the iris would be suggestive of such an origin. The finding of a nevus involving both the iris and the ciliary body, on the other hand, is consistent with a primary tumor in both sites.

In an extensive study of uveal melanomas, Raivio[5] reported that of three patients who refused operation at the time of diagnosis, two had survived more than 20 years (one died of an unrelated cause one year after diagnosis). Koenig[6] described a case of iris melanoma occurring in a one-eyed patient. To preserve vision, the tumor was left untouched for 20 years, until the patient died of a myocardial infarction at the age of 77 years. At autopsy, the malignant melanoma of the iris was confirmed, and there was no evidence of metastasis. Cleasby[7] and Freyler[8] have described a patient with an iris melanoma which was initially incompletely excised with a sector iridectomy. Between 22 and 23 years later, problems related to the recurrence of the tumor necessitated an enucleation in both patients. Despite extension of the tumors throughout the anterior segment and into the subconjunctival region, neither of the patients had clinical evidence of distant spread.

Currently, there is no way to predict which of these malignancies will invade only locally, and which will result in widespread metastases. The reasons iris melanomas tend to be less lethal than melanomas of the choroid and ciliary body are not known. We think that the aqueous humor does not affect growth inhibition, simply because in our case and others the melanomas remained slow-growing, even in areas distant from the aqueous chambers.

Summary

A patient with spindle melanoma involving the iris and ciliary body refused enucleation at the time of diagnosis in 1933. The eye developed painful glaucoma 13 years later and was enucleated. Histopathologic examination indicated spread of the tumor intrasclerally and subconjunctivally. The patient is still alive without evidence of metastases, 32 years after enucleation and 45 years after initial diagnosis.

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MALIGNANT MELANOMA OF THE CHOROID IN NEUROFIBROMATOSIS

ROBERT A. WIZNIA, M.D., JEROME K. FREEDMAN, M.D.,
AND ANTHONY D. MANCINI, M.D.

New Haven, Connecticut

AND

JERRY A. SHIELDS, M.D.

Philadelphia, Pennsylvania

Hamartomas of the retina and uveal tract occur in patients with neurofibromatosis (von Recklinghausen's disease). These are mainly glial or melanocytic hamartomas, but there may be variable degrees of each.[1] Although the incidence of uveal melanomas in patients with neurofibromatosis is higher than in the general population,[2] most melanomas involve the iris and to our knowledge only four cases of choroidal malignant melanoma associated with neurofibromatosis have been reported.[3–6] We describe herein the case of a patient with neurofibromatosis, multiple iris hamartomas, and an unusual malignant melanoma of the choroid, characterized by extensive central necrosis. This case emphasizes the need to consider malignant melanoma in the differential diagnosis of fundus lesions in patients with neurofibromatosis.

CASE REPORT

A 60-year-old white woman with multiple skin lesions characteristic of neurofibromatosis distributed over much of her face, extremities, chest, and abdomen was referred in February 1977 for evaluation of choroidal mass lesions and secondary neurosensory retinal detachment in the left eye, which caused a progressive decrease in vision over a one-month period. A 5- to 6-disk diameter, slightly elevated choroidal mass lesion, was evident in the inferior fundus in July 1974 and February 1975. During earlier examinations, visual acuity was 6/6 (20/20) in both eyes and the lesion was stable with no overlying neurosensory retinal detachment.

On Feb. 17, 1977, best corrected visual acuity was R. E.: 6/6 (20/20), and L. E.: 6/21 (20/70). The visual field in the left eye was absent superiorly. Multiple nodular skin lesions were present on the face, including both eyelids. There were numerous, slightly elevated, brown nevi in both irides. Ophthalmoscopic examination of the right eye was unremarkable. Ophthalmoscopic examination of the left eye revealed a sensory retinal detachment inferiorly extending along the ora serrata from 4 to 8 o'clock and posteriorly to the optic disk and inferior macula. Beneath the detachment was a choroidal mass measuring 9 × 7 disk diameters and extending inferiorly from the optic disk and macula (Fig. 1). Its color was gray-brown with some yellowish mottling. The central portion of the lesion was nonpigmented and depressed, giving the entire lesion a donut configuration. This central area contained large choroidal vessels. Transillumination was blocked by the dense pigmentation of the mass, except in the central nonpigmented area.

Fluorescein angiography of the mass revealed multiple hyperfluorescent foci during the arteriovenous phase and progressive leaking, which resulted in marked staining of the mass and the overlying serous fluid in the later angiograms. The angiographic findings were compatible with a choroidal melanoma. Contact B-scan ultrasonography demonstrated a shallow sensory retinal detachment, and underlying choroidal mass, with an acoustically distinct inner boundary, low internal reflectivity, and choroidal excavation. This finding was compatible with a choroidal melanoma.

Evaluation included x-rays of the chest and abdomen, an intravenous pyelogram, upper gastrointestinal series, and a barium enema, all of which were negative for metastases. A brain scan was normal. Liver and spleen scans revealed patchy activity caused by a parenchymal disease such as cirrhosis. The urine was negative for melanogens. Routine hematologic and blood chemistry tests were unremarkable.

On the basis of the findings, the left eye was enucleated in March 1977. There has been no recurrence of tumors since that time. Pathologic examination revealed a normal-sized globe. Inferior to the optic disk was a bilobed choroidal mass, with the two lobes separated by a dense plaque of fibrous connective tissue containing abundant blood vessels and necrotic tumor cells (Fig 2). Overlying the

From the Retina Service, Division of Ophthalmology, Department of Surgery (Drs. Wiznia and Freedman), and the Department of Medicine (Dr. Mancini), Hospital of St. Raphael, New Haven, Connecticut, and the Oncology Unit, Retina Service, Wills Eye Hospital, Philadelphia, Pennsylvania (Dr. Shields). This study was supported in part by the Retina Research and Development Foundation, Philadelphia, and the Lions Club of Pennsylvania.

Reprint requests to Robert A. Wiznia, M.D., 850 Howard Ave., New Haven, CT 06519.

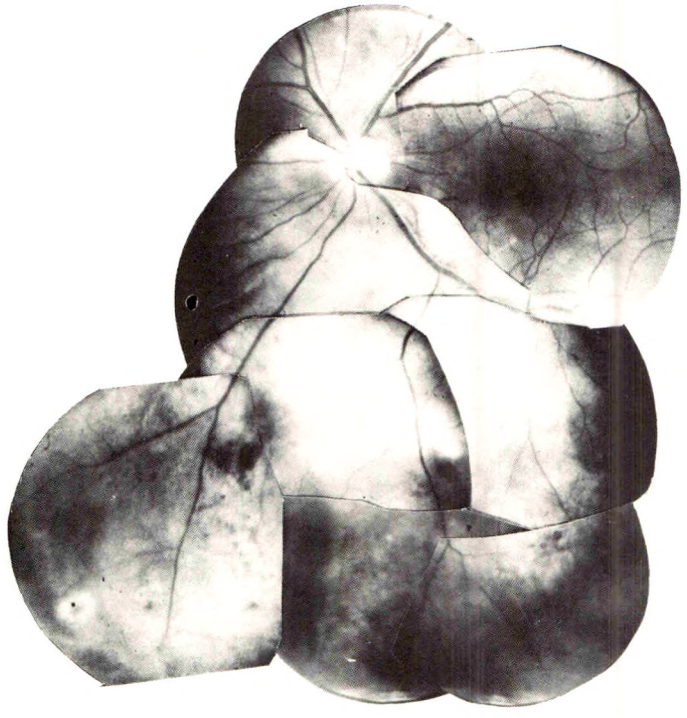


Fig. 1 (Wiznia and associates). Choroidal mass located inferior to optic disk. There is a donut appearance caused by central atrophy.

central fibrous portion of the tumor was a large intraretinal cyst. Smaller intraretinal cysts were present over the inferior portion of the tumor. Posteriorly, the tumor cells extended along the perineural sheaths in the mid-portion of the sclera, but there was no extraocular extension. The tumor was composed almost entirely of oval-shaped cells with round distinct nuclei and prominent nucleoli, characteristic of spindle B malignant melanoma cells (Fig. 3). Occasional mitotic figures were present. The multiple melanocytic hamartomas (nevi) located on the anterior border layer of the iris correlated with the elevated iris nevi evident from slit-lamp examination (Fig. 4).

Discussion

This case demonstrates the occurrence of malignant melanoma of the choroid in a patient with neurofibromatosis, and emphasizes the importance of considering this diagnosis when a choroidal mass is evident in such patients. Recent reports have discouraged an enucleation for small pigmented choroidal lesions.[7–9] We



Fig. 2 (Wiznia and associates). Low power photomicrograph of mass demonstrated its bilobed appearance separated by a dense plaque of fibrous connective tissue (hematoxylin-eosin × 50).

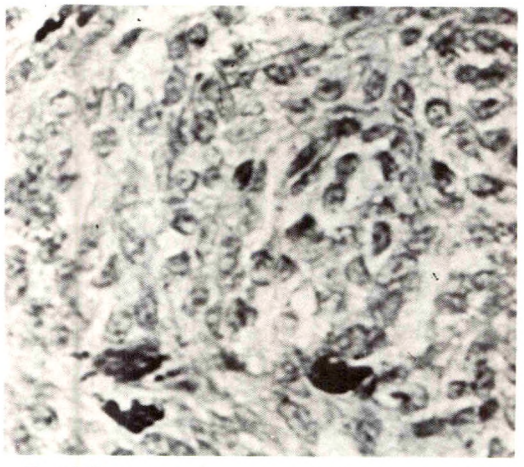


Fig. 3 (Wiznia and associates). High power photomicrograph, showing cells within choroidal mass (hematoxylin-eosin × 300).

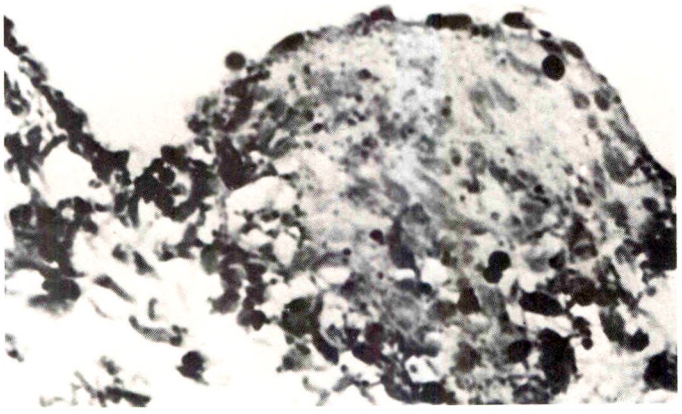


Fig. 4 (Wiznia and associates). High power photomicrograph of melanocytic hamartoma on the anterior surface of the iris (hematoxylin-eosin × 350).

waited until there was clinical evidence of tumor enlargement before enucleating the eye.

Our case raises the question of the differential diagnosis of a fundus mass in a patient with neurofibromatosis. Entities to be considered include glial hamartoma of the retina,[10] choroidal neurofibroma,[11] choroidal nevus,[12] and choroidal melanoma.[3-6] The glial hamartoma (astrocytoma) should present no diagnostic problem, for it is retinal rather than choroidal in location, white rather than pigmented, and identical to lesions noted in tuberous sclerosis.[2] A choroidal neurofibroma or a large nevus may be impossible to distinguish from a malignant melanoma, both clinically and histologically.[13] In such cases, therefore, a period of observation for growth seems justified. This approach supported the diagnosis of malignant melanoma in our case.

The neuroectodermal origin of nevus cells may explain the increased number of uveal nevi found in patients with neurofibromatosis. Choroidal melanomas probably arise from pre-existing nevi rather than from the Schwann cells of the ciliary nerves.[6] We believe that the greater number of pre-existing nevi in patients with neurofibromatosis may predispose these patients to a slightly higher incidence of uveal melanomas.

Microscopic examination revealed an area of fibrovascular connective tissue with residual tumor cells in the center of the malignant melanoma. The appearance was similiar to that of a case cited by Gass,[14] but that case did not involve neurofibromatosis (personal communication, 1978). This finding may be related to a previous episode of spontaneous regression or necrosis within the tumor. Jensen and Anderson[15] reported a case of choroidal lesions that showed scleral invasion and large areas of fibrosis and calcification. A few neoplastic melanocytes could be identified. We believe our case represents a less advanced but similiar process of tumor regression. Our patient had no tumor recurrence for 15 months after enucleation.

Summary

A 60-year-old white woman with generalized neurofibromatosis and multiple melanocytic hamartomas of the iris developed an unusual choroidal mass, with secondary sensory retinal separation in the left eye. Ophthalmoscopically the tumor had a peculiar donut configuration that was caused by a large focus of central necrosis within a spindle B melanoma.

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ASTROCYTIC HAMARTOMA OF THE RETINA NOT ASSOCIATED WITH TUBEROUS SCLEROSIS

FREDERICK H. REESER, M.D., THOMAS M. AABERG, M.D.,
AND
DIANE L. VAN HORN, PH.D.
Milwaukee, Wisconsin

Although astrocytes are profuse in the retina and the optic nerve, tumors of astrocytic origin in these locations are rare. They may occur in association with tuberous sclerosis, neurofibromatosis, or as an intraocular extension of an optic nerve glioma,[1–3] and may simulate other causes of leukocoria, including retinoblastoma. The absence of confirmatory systemic lesions of tuberous sclerosis in the infant or young child may make a correct diagnosis more difficult.

We describe herein the unusual occurrence of a retinal astrocytic hamartoma not associated with tuberous sclerosis, which appeared to enlarge and involve the optic nerve. The lesion was irradiated, which led to an extensive secondary retinal detachment and a marked loss of vision. Because of the continuing poor vision and evidence of optic nerve involvement on computed tomography, the eye was enucleated and examined by light and electron microscopy.

CASE REPORT

An 11-year-old boy who complained of decreased vision in the left eye was examined here June 20, 1973. Five years previously he had been hit on the left side of the head with a baseball bat. At that time he was examined by an ophthalmologist who noted a moderately elevated yellowish white retinal lesion temporal to the disk in the left eye (Fig. 1). The clinical diagnosis of a retinal astrocytoma was made, although no other evidence of phakomatoses could be found in either the patient or his family. Subsequent examinations by the referring physician revealed a slight increase in the size of the lesion and a mild decrease in the visual acuity in the left eye. An easily controlled seizure disorder appeared, although no seizures occurred after 1971.

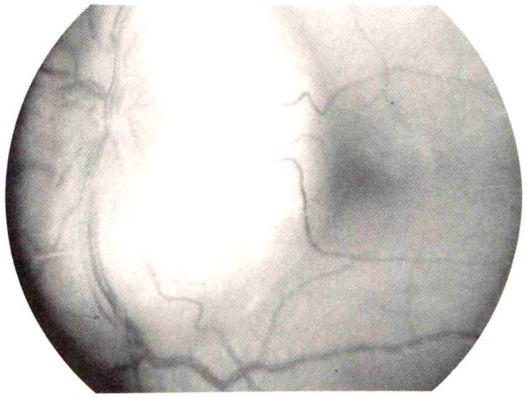


Fig. 1 (Reeser, Aaberg, and Van Horn). Moderately elevated, slightly nodular, retinal mass that extends from the disk to the nasal side of the macula. This is the lesion's appearance in 1969.

On examination in 1973, the patient was in good health, with no dermatologic or neurologic evidence of tuberous sclerosis. Visual acuity was R.E.: 6/6 (20/20); L.E.: 6/15 (20/50). The right eye was normal, and the abnormalities in the left eye were confined to the posterior pole. A relatively large, moderately elevated yellowish-white lesion extended from the temporal margin of the optic disk to the center of the macula. The mass obscured the underlying retinal details. Exudates and minimal subretinal fluid were noted along the margins of the lesion, and mulberry-shaped excrescences, which had not been as prominent in the original fundus photographs taken in 1968, were in the substance of the mass. Observers concurred with the diagnosis of a retinal astrocytic hamartoma.

Additional growth of the retinal lesion was documented during the following two years with apparent extension nasal to the disk (Fig. 2) as well as above and below the temporal vascular arcades and into the macula (Fig. 3). The mass remained yellowish-white with portions appearing deep to the retinal vessels, whereas other portions obscured the retinal vessels. Transient nerve fiber layer hemorrhages were noted, and the exudate-like satellite lesions along the periphery of the main tumor increased in number. The optic nerve papilla itself

From the Medical College of Wisconsin Eye Institute, Milwaukee, Wisconsin.

Reprint requests to Frederick H. Reeser, M.D., the Medical College of Wisconsin Eye Institute, 8700 W. Wisconsin Ave., Milwaukee, WI 53226.

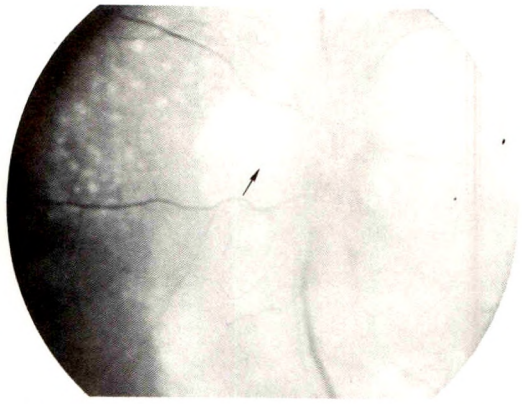


Fig. 2 (Reeser, Aaberg, and Van Horn). The retinal lesion in 1975 involves the disk and extends across into the nasal retina (arrow).



Fig. 4 (Reeser, Aaberg, and Van Horn). The computed tomography demonstrates increased density within the posterior aspect of the globe and increased prominence of the optic nerve on the left (arrow).

appeared to be involved. On Aug. 8, 1976, computed tomography, done for the second time with and without contrast enhancement, revealed no evidence of tuberous sclerosis in the central nervous system, but demonstrated increased density in the posterior aspect of the left globe and increased prominence of the left optic nerve posterior to the globe as compared to the right optic nerve (Fig. 4). Tomograms of the optic canals were normal. A screening of the patient's parents for phakomatoses, including computed tomography, was negative.

Fluorescein angiography performed in 1976 demonstrated a multitude of vessels in the lesion. There were numerous aneurysmal dilatations associated with these vessels (Fig. 5), which also involved the optic disk and leaked profusely in the later phases of the angiogram (Fig. 6).

After consultation with other centers, we decided to irradiate the posterior aspect of the left globe because of the increasing size of the lesion without other definite evidence of tuberous sclerosis, the reduction of visual acuity to 6/60 (20/200), and the presumed extension of the tumor into the optic nerve itself (Fig. 7). In October 1976, the patient received 3,000 rads of irradiation to the retina in 12 fractions during 34 days. The treatment was given with a 6-mV linear accelerator with a single lateral

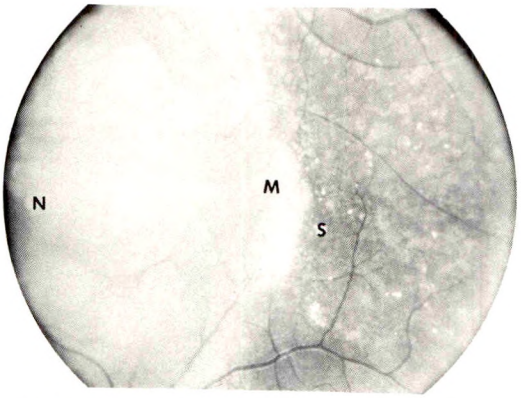


Fig. 3 (Reeser, Aaberg, and Van Horn). The tumor in 1975 temporal to the disk. It now extends into the macula (M) with calcified nodules (N) and yellowish-white satellite lesions(S).

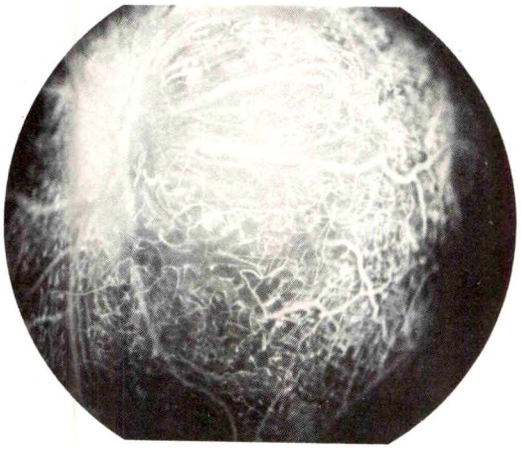


Fig. 5 (Reeser, Aaberg, and Van Horn). Fluorescein angiogram shows a multitude of tumor vessels. These vessels are tortuous with aneurysmal dilations.

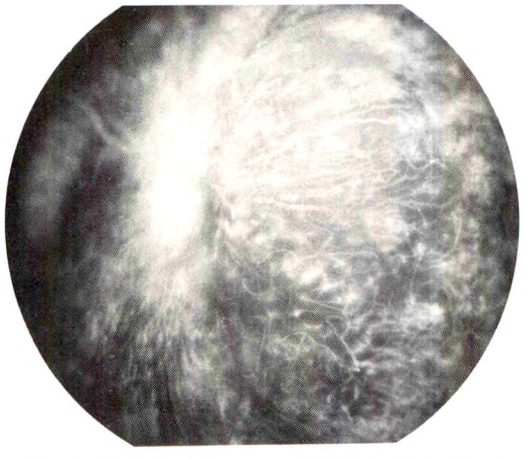


Fig. 6 (Reeser, Aaberg, and Van Horn). A slightly later phase of the fluorescein angiogram demonstrates diffuse leakage of fluorescein from the abnormal tumor vessels.

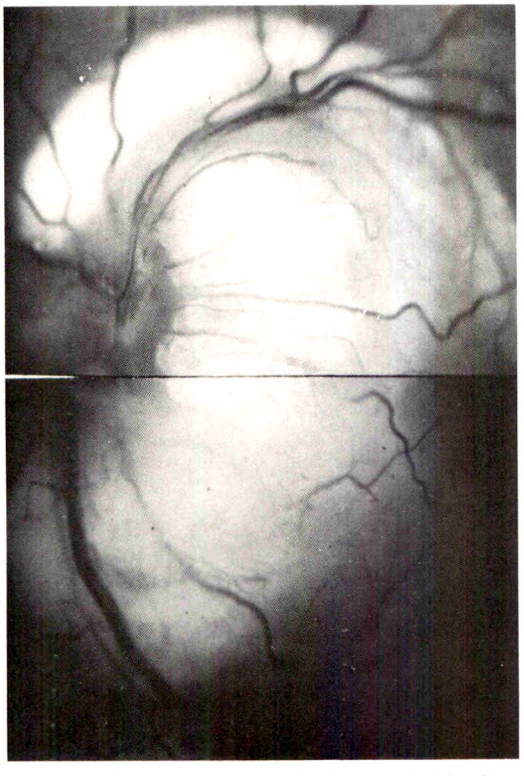


Fig. 7 (Reeser, Aaberg, and Van Horn). The fundus lesion in March 1976 shows continued growth with extension through the macula. The tumor appears more nodular and calcified, especially immediately temporal to the optic disk.

field. After irradiation of the left eye, the visual acuity rapidly deteriorated to hand motion and a large exudative retinal detachment developed (Fig. 8). This detachment largely resolved in the next several months, but the vision remained markedly reduced.

The left eye was enucleated Nov. 29, 1976, because we still believed that the tumor extended posteriorly into the optic nerve, and the visual acuity had apparently decreased permanently. We made several openings into the enucleated globe in the region of the pars plana to allow the fixative to enter the vitreous cavity, and placed the eye in 2.7% glutaraldehyde in phosphate buffer (pH 7.2, 330 m0sm.).

Results

On gross examination, the eye was of normal size and shape. Eight millimeters of optic nerve was attached to the globe, and the nerve appeared normal. A light transmission defect was present surrounding the optic disk. The eye was opened horizontally after the optic nerve stump had been removed. A firm, white mass measuring 8 mm wide, 7 mm long, and 3 mm high was present surrounding the optic disk (Fig. 9). The tumor blended into the substance of the proximal optic nerve, and it was gritty on its cut surface. A portion of the tumor was submitted for transmission electron microscopy.

On light microscopic examination, the abnormalities were confined to the retina



Fig. 8 (Reeser, Aaberg, and Van Horn). The posterior pole of the left eye with an extensive, secondary retinal detachment (1976). Nerve fiber layer hemorrhages are present (arrow).

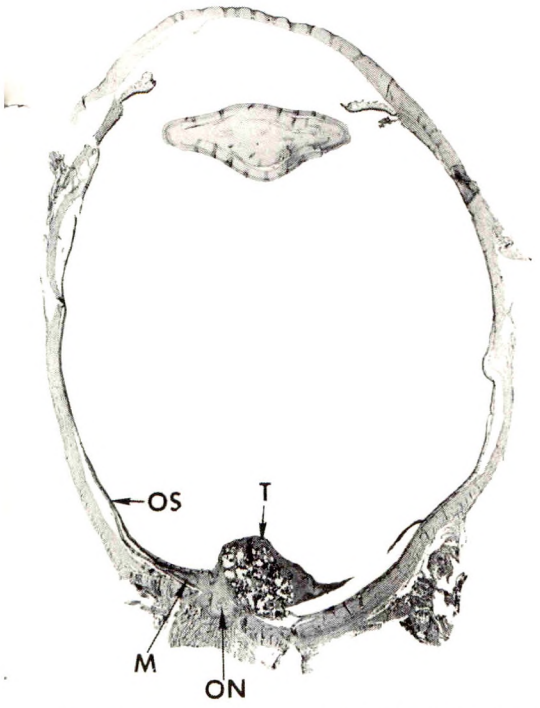


Fig. 9 (Reeser, Aaberg, and Van Horn). Whole left eye sectioned horizontally (hematoxylin and eosin, ×5). The astrocytic hamartoma (T) is noted to blend into the substance of the proximal optic nerve (ON). Subretinal macrophages (M). The retina with its lack of outer segments (OS).

and the optic nerve. The tumor was located within the substance of the retina and optic disk, and the retinal portion was covered by an intact internal limiting membrane. The cells in the mass appeared to consist of tightly packed astrocytes with round or oval nuclei, eosinophilic cytoplasm, and indistinct cell borders (Fig. 10). No mitotic figures were seen in the tumor. Electron microscopy revealed that the intact astrocytes contained closely packed filaments. Other cells were edematous and appeared electron-lucent (Fig. 11).

In the tumor, especially on the temporal edge of the disk, were large collections of amorphous material and calcium (Figs. 12 and 13). The tumor appeared relatively avascular. In the optic nerve, just anterior

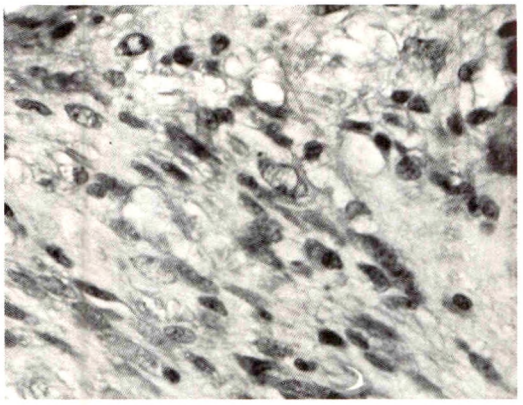


Fig. 10 (Reeser, Aaberg, and Van Horn). Light micrograph of astrocytic cells within the tumor (hematoxylin and eosin, ×430).

to the lamina cribrosa, more typical drusen were present (Fig. 14). The optic nerve apparently was not involved, except for the more superficial portions of the nerve head (Fig. 15). A large collection of macrophages lay under the retina (Fig. 16), especially on the nasal side of the disk, which perhaps accounted for the clinical appearance of exudates along the margins of the tumor. Transmission electron microscopy revealed that the macrophages were filled with clear vacuoles and residual bodies (Fig. 17).

There was a profound loss of outer segments throughout most of the retina and not merely confined to the region of the tumor (Fig. 18). Transmission electron microscopy demonstrated that the inner segments of the photoreceptors rested on the pigment epithelial cells. In some areas, the junctional complexes of the outer limiting membranes could be seen between the inner segments and the pigment epithelial cells (Fig. 19).

Discussion

Astrocytic hamartomas of the retina and optic disk are considered to be congenital lesions and represent anomalies of tissue formation and maturation.[4] They originate from tissue normally present in the

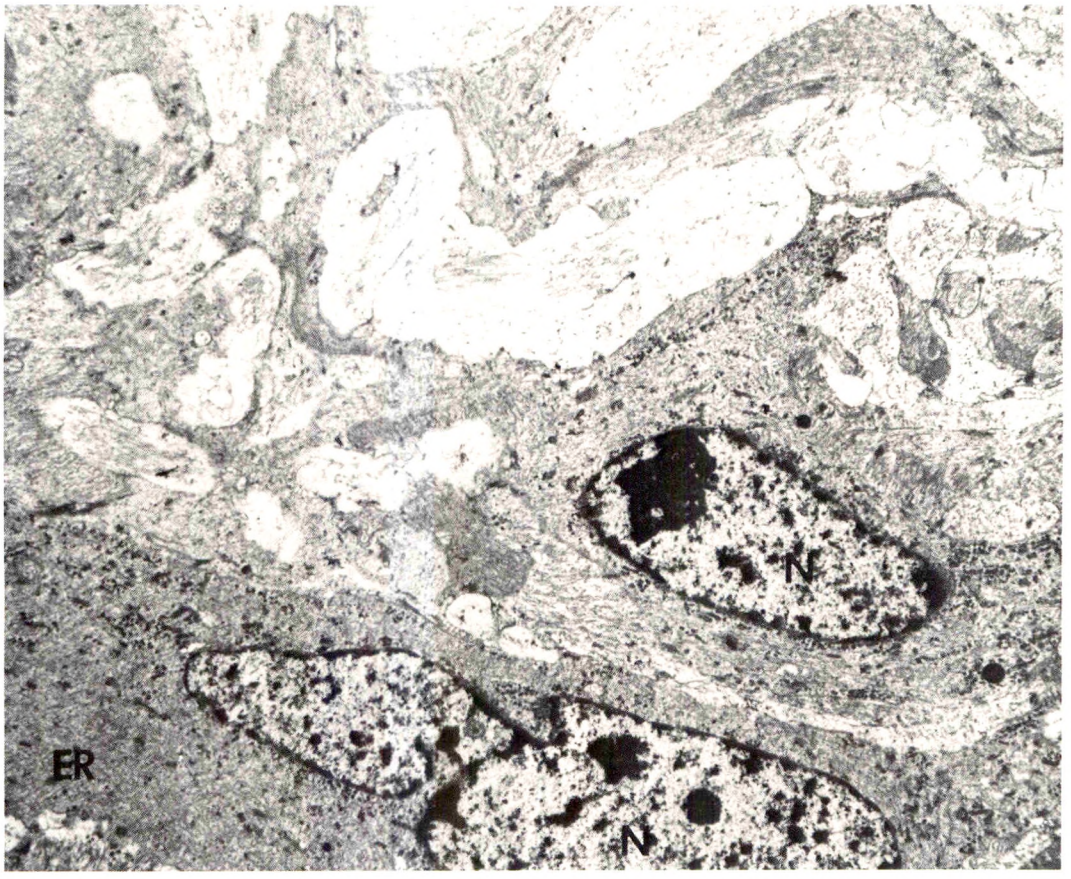


Fig. 11 (Reeser, Aaberg, and Van Horn). Transmission electron micrograph of astrocytes in area of tumor. The intact cells contain closely packed filaments, nuclei (N), and a few elements of rough endoplasmic reticulum (ER). Other cell processes are edematous (×5,225).

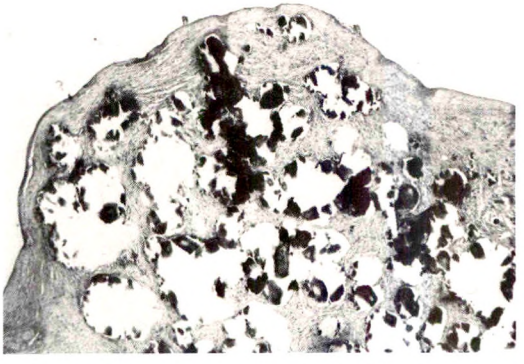


Fig. 12 (Reeser, Aaberg, and Van Horn). A large collection of calcium and hyaline is noted within the astrocytic hamartoma (hematoxylin and eosin, ×250).

site: in our case, the tissue was the astrocyte, which, however, was never normal. This is not a true neoplasm, which is an overgrowth of tissue that was originally normal. These astrocytic hamartomas of the retina and optic disk are frequently associated with tuberous sclerosis. Although they are not considered to be a part of the classic triad of mental retardation, seizures, and adenoma sebaceum, retinal and optic disk hamartomas occur in over one half of the patients with this disease.[5,6]

The patient in our study was not considered to have tuberous sclerosis. However, the pathologic abnormalities that

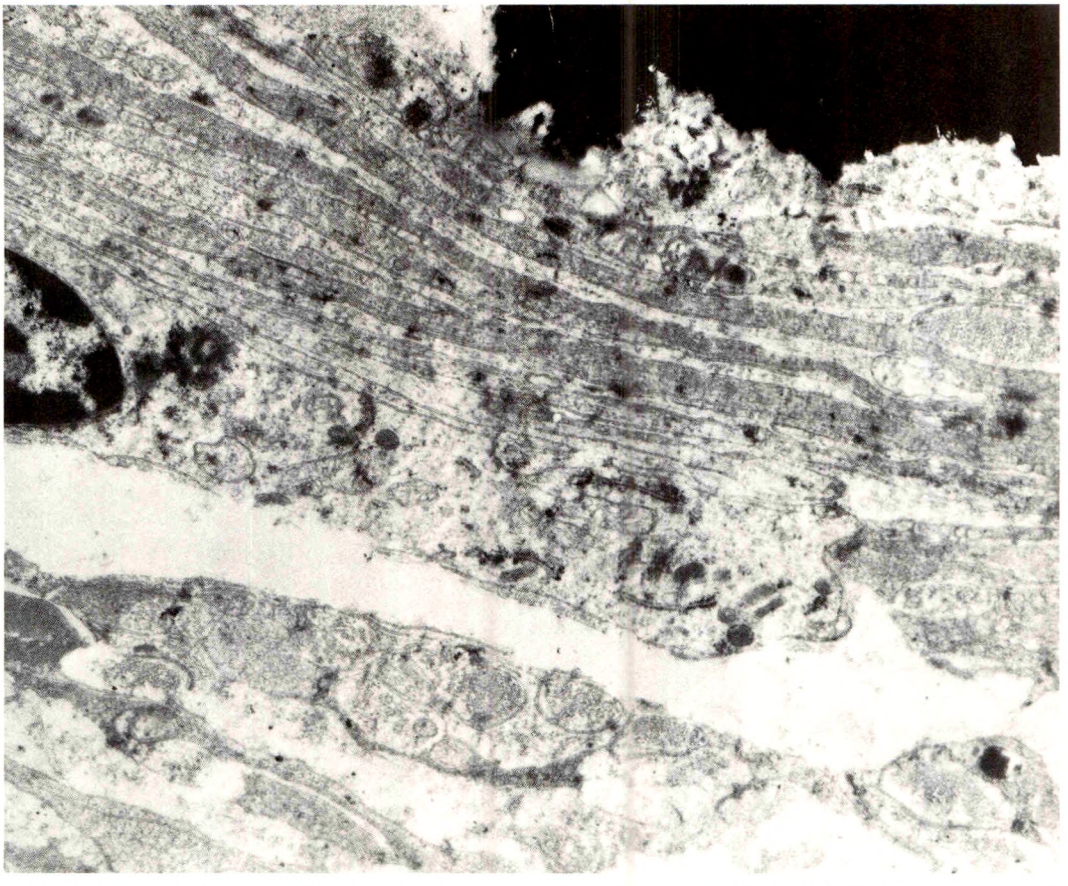


Fig. 13 (Reeser, Aaberg, and Van Horn). Transmission electron micrograph of calcific deposit (upper right) and its surrounding astrocytic processes (×14,125).

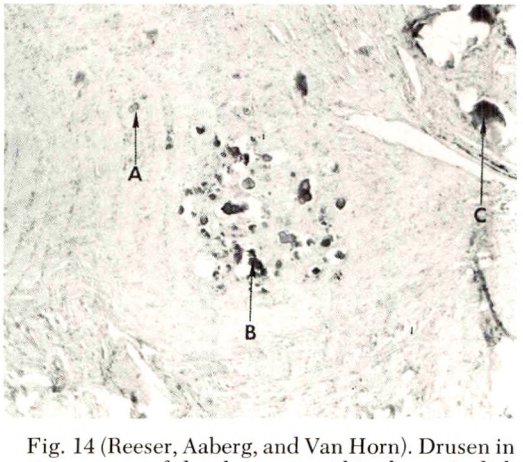


Fig. 14 (Reeser, Aaberg, and Van Horn). Drusen in various stages of development within the optic disk and proximal optic nerve. These show a continuum from the smallest (A) through a collection of intermediate size (B) to the large, giant drusen, associated with an astrocytic hamartoma (C) (hematoxylin and eosin, ×250).

lead to such a diagnosis have still not been clearly defined and may not be discovered until an autopsy is performed. One example of this is embryonal mixed

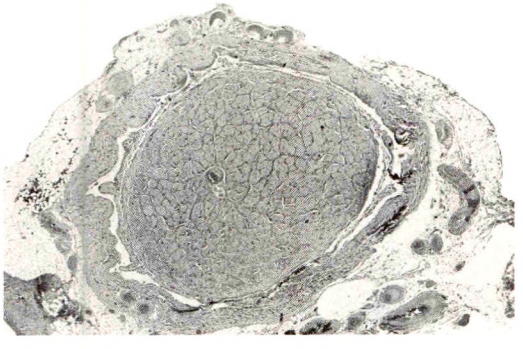


Fig. 15 (Reeser, Aaberg, and Van Horn). The optic nerve immediately posterior to the globe is essentially normal (hematoxylin and eosin, ×40).

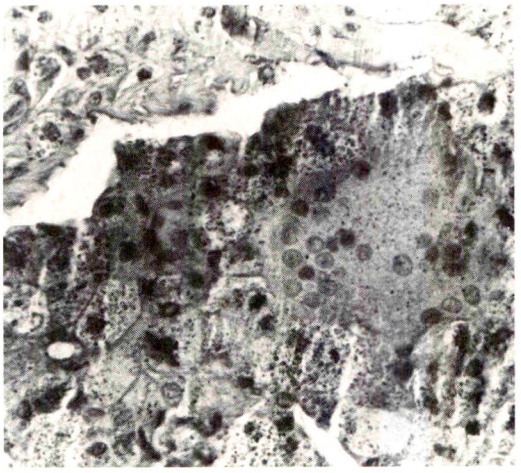


Fig. 16 (Reeser, Aaberg, and Van Horn). A subretinal collection of macrophages surrounding the disk. The underlying retinal pigment epithelium is normal (hematoxylin and eosin, ×430).

tumors of the kidney that occur in 80% of patients with tuberous sclerosis, yet are rarely diagnosed during the patient's lifetime.[7] Some investigators contend that the presence of an astrocytic hamartoma of the retina is sufficient evidence to make the diagnosis of tuberous sclerosis.[8] These retinal tumors have been present, presumably as the only finding in a family member, when a number of siblings had more complete forms of tuberous sclerosis.[9] Foos,[1] on the other hand, does not consider isolated retinal astrocytomas to be hamartomas in the absence of other associated developmental anomalies.[1] To diagnose tuberous sclerosis, the physician must know and search for its various manifestations. Numerous cutaneous expressions of the disease have been reported: the more common adenoma sebaceum, shagreen patches found most commonly in the lumbar region, white "ash leaf" lesions present early in life but often overlooked unless a search for them is made with a Wood's light,[10] subungual fibromas, café au lait spots, and vitiligo.[11] Our patient and his family were scrutinized for these and other findings associated with tuberous sclerosis; however, none was found, with the exception of the easily controlled seizure disorder that appeared after a head trauma at 6 years of age and lasted only three years.

Occasional studies have described astrocytomas or astrocytic hamartomas in the eye that were not believed to be associated with either tuberous sclerosis, neurofibromatosis, or intraocular extension of an optic nerve glioma.[1–3, 12–14] Several of these eyes were removed because of the mistaken diagnosis of retinoblastoma at an early age before certain of the other signs and symptoms of tuberous sclerosis might have manifested themselves.[3] Adenoma sebaceum, for instance, is found in over 80% of cases of tuberous sclerosis,[5] but does not usually manifest itself until the age of 2 to 6 years.[11] The differentiation of a retinal astrocytic hamartoma from a retinoblastoma may present a diagnostic problem.[3] Most retinal hamartomas are noted as part of the syndrome of tuberous sclerosis at an age when a retinoblastoma would be unlikely. The average age of diagnosis of tuberous sclerosis is 8 years in retarded patients and 17 years in nonretarded patients,[5] whereas the average age of diagnosis in retinoblastoma patients is 2 years.[15] Additionally, the retinal astrocytic hamartoma usually spares the macula, making its early diagnosis less likely. The astrocytic hamartoma has a limited growth potential,[16] and rapid progression in size is unusual,[17] which would suggest the need for close observation rather than enucleation when confusion exists. Other diagnostic studies may be indicated in selected cases, such as the measurement of lactic acid dehydrogenase activity in the aqueous humor because this may markedly increase in eyes with retinoblastoma.[18,19]

Retinal inflammation or ocular trauma resulting in retinal hemorrhage may

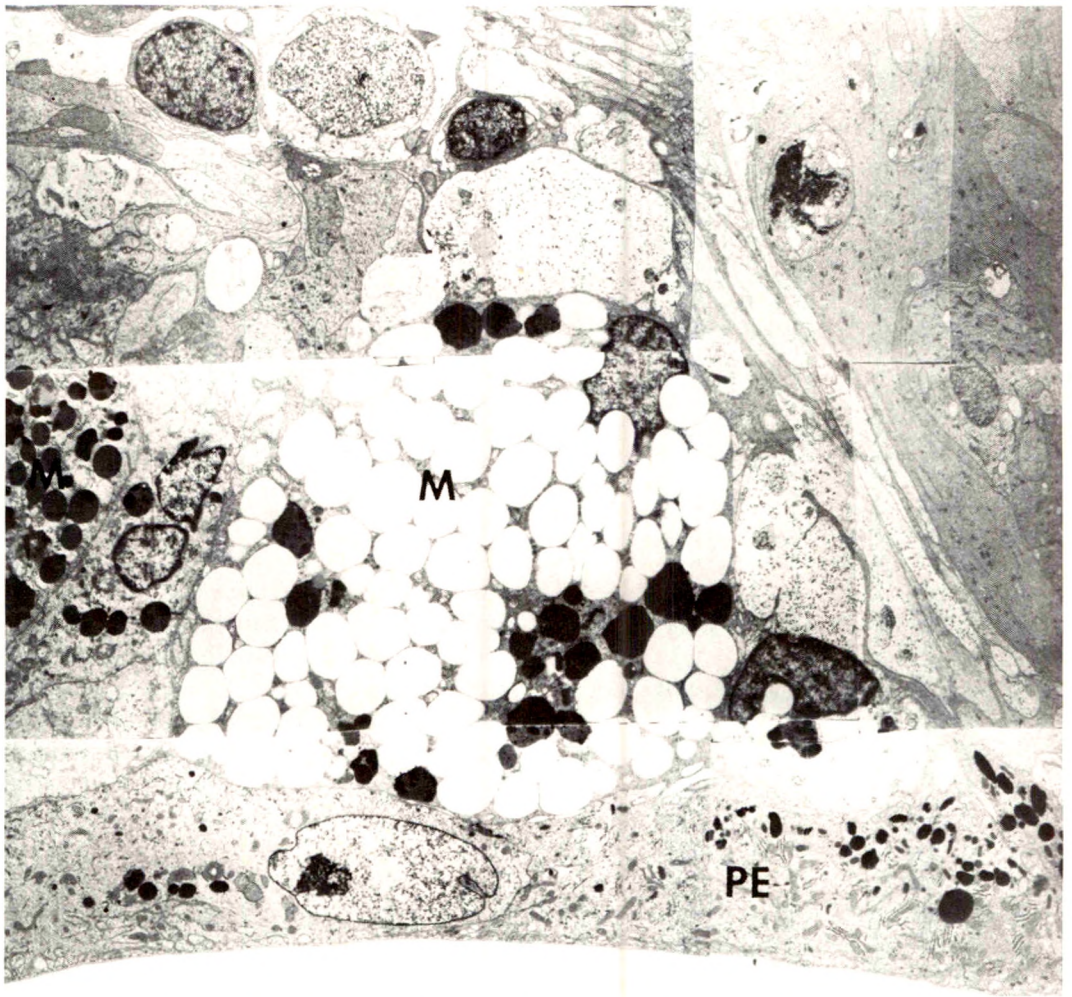


Fig. 17 (Reeser, Aaberg, and Van Horn). Montage of pigment epithelial cells (PE), subretinal macrophages (M), and a portion of the tumor (upper right corner). The macrophaes are filled with clear vacuoles and residual bodies (×3,000).

lead to secondary retinal gliosis and fibrosis, which may be confused with a tumor.[15] When examined at the time of the head trauma, our patient had a retinal mass without evidence of hemorrhage or ocular inflammation. Because of the lack of microscopic and clinical evidence of ocular trauma as well as the presence of giant drusen within the tumor, we concluded that this lesion was not a form of secondary astrocytic proliferation.

As the retinal astrocytic hamartoma ages, it assumes a more elevated nodular or "mulberry" appearance,[17] evidently caused by the increasing calcification of the lesion. This nodular appearance is usually associated with an older lesion, but at times occurs in infants several months old.[17] The evolution of the lesion in our case is well demonstrated when the earlier lesion (Fig. 1) is compared with the same lesion seven years later (Fig. 7).

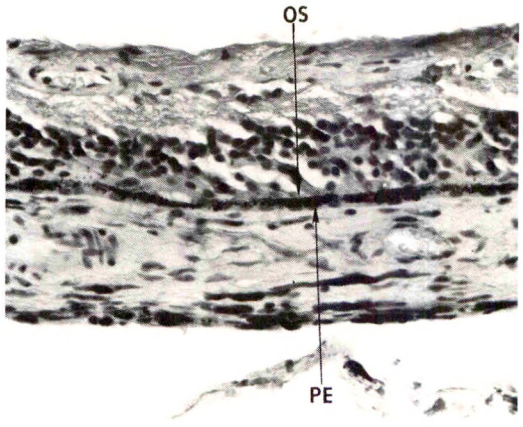


Fig. 18 (Reeser, Aaberg, and Van Horn). The outer segments (OS) of the retinal photoreceptors are virtually absent, whereas the retinal pigment epithelium (PE) is present (hematoxylin and eosin, ×250).

Retinal astrocytic hamartomas generally originate from the inner surface of the retina or optic nerve head, but may on occasion involve the deeper layers of the retina. Gass[20] described a case similar to ours of a 15-year-old boy who had a large exophytic astrocytic retinal hamartoma without other clinical evidence of tuberous sclerosis.[20]

The presence of retinal tumors that are clinically similar, if not identical to those associated with tuberous sclerosis are infrequently found in patients with neurofibromatosis.[21–24] This condition must therefore also be ruled out when a patient has a retinal mass such as the one reported here.

In previous reports,[1–3, 12–14] retinal and optic disk astrocytomas or astrocytic hamartomas not associated with tuberous sclerosis or neurofibromatosis clearly arose from the optic nerve head and only involved the retina secondarily.[1,13] The case reported by Cleasby[3] was similar to our case, including the presence of satellite lesions although the patient was only 20 months old when the eye was enucleated for a suspected retinoblastoma. The subsequent development of other signs of tuberous sclerosis may have taken place as was the case in the patient reported by McLean[12] in 1935, the first case of a "true glioma of the retina." However, the patient later displayed evidence of tuberous sclerosis, which led to institutionalization.[25] Because a retinal astrocytic hamartoma unassociated with other signs of phakamotoses is rare, it is difficult to diagnose tuberous sclerosis when only retinal lesions are present.

The fluorescein angiography done in our case demonstrated an abundance of tumor vessels with multiple aneurysmal dilatations and coincident vessel leakage. This leakage may have been related to the drusen formation in the tumor mass and optic nerve head.

The retinal tumor in our case grew relatively rapidly which made us suspect that it was astrocytoma.[1] Additionally, computed tomography revealed proximal nerve involvement; we therefore administered radiation therapy. This mode is occasionally effective in the treatment of astrocytomas that occur elsewhere in the central nervous system. Following the administration of 3,000 rads to the area of the retinal and optic disk tumor, an exudative detachment and a marked reduction in visual acuity developed. The detachment had largely subsided by the time the eye was enucleated; however, the visual acuity had not improved. The discrepancy between the apparent optic nerve enlargement on computed tomography and its lack of involvement in the enucleated specimen could not be explained even with re-examination of the tomogram.

Microscopic examination of the enucleated specimen revealed no evidence of significant tumor extension into the optic nerve. The tumor was composed of benign-appearing astrocytes with a relatively sparse vasculature and large deposits of calcium and hyaline. There were, however, several unexpected microscopic findings. There were large collections of macrophages beneath the retina, especial-



Fig. 19 (Reeser, Aaberg, and Van Horn). Transmission electron micrograph illustrating lack of outer segments of the photoreceptors. The junctional complexes (arrows) of the outer limiting membrane of the retina are between the inner sements and the anterior cell membrane of the pigment epithelial cells. Macrophages (M) are seen in the retina (×7,100).

ly on the nasal side of the disk. These macrophages may have been partially responsible for the appearance of apparently rapid tumor growth and the satellite lesions surrounding the border of the tumor before irradiation. On the other hand, they may have resulted from radiation-induced necrosis. Additionally, there was an almost total loss of the outer segments of the photoreceptors in the presence of a largely attached retina, a relatively normal pigment epithelium, and no evidence of tapetoretinal degeneration. Retinitis pigmentosa is sometimes associated with peripapillary drusen.[26,27] This outer segment loss may have also been a result of the irradiation, although the photoreceptors are usually considered to be relatively resistant to radiation. On the other hand, the loss may have been related to the transient secondary retinal detachment, especially if there was a significant inflammatory response. On transmission electron microscopy, the macrophages contained clear vacuoles that could have been lipid (extracted during processing). This lipid may have resulted from digested outer segments as the pigment epithelium contained few phagolysosomes or remnants of outer segments.

Nonetheless, this degree of outer retinal loss generally does not occur with inflammatory or secondary detachments, especially when the retinal pigment epithelium appears essentially normal.

SUMMARY

A 6-year-old boy had a peripapillary lesion diagnosed as retinal astrocytic hamartoma, which was not associated with tuberous sclerosis, neurofibromatosis, or intraocular extension of a glioma. The patient was observed for nine years, during which time the lesion grew significantly. Because of this growth and the evidence of proximal optic nerve involvement on computed tomography, radiation therapy was administered with a resultant marked reduction in visual acuity. The eye was subsequently enucleated.

The enucleated eye was studied by both light and transmission electron microscopy. The specimen had a retinal astrocytic hamartoma with sparse vascularization and only superficial optic nerve involvement. Additionally, it revealed optic nerve drusen in varying stages of development, significant accumulations of subretinal macrophages, and an almost total loss of retinal outer segments with the preservation of the retinal pigment epithelium.

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SEBACEOUS GLAND CARCINOMA OF THE EYELID

ELLIOT PERLMAN, M.D., AND ROBERT T. MCMAHON, M.D.

New Haven, Connecticut

Sebaceous gland carcinoma may arise from the Meibomian and Zeiss glands, the sebaceous glands which drain into hair follicles present in the skin of the eyelid and eyebrow, and the sebaceous glands of the caruncle.[1] Although advanced cases of this neoplasm have been primary orbital tumors, we believe that both the significant degree of orbital involvement and the coexistent occlusion of the central retinal artery, which were present in our case, constitute rare instances of sebaceous gland carcinoma of the eyelid.

CASE REPORT

An 82-year-old white man was admitted to the hospital on Oct. 25, 1977, with a two-month history of increased redness and swelling of his right eye, which was associated with tearing and decreased vision. His past eye and medical histories were unremarkable. He complained of decreased appetite during the previous few weeks.

Examination revealed visual acuity was light perception with fair projection in the right eye, and 6/7.5 (20/25) in the left eye. Proptosis of the right eye was 11 mm more than the left eye (Fig. 1). The right upper eyelid was blepharoptic and rested on a chemotic and hemorrhagic conjunctiva. Both the right eyelid margin and the number of cilia of the right eyelids were comparable to the left eyelids. A hard, granular, palpable mass infiltrated the lateral aspects of both upper and lower eyelids on the right side.

A right afferent pupillary defect was present. There was also a total external ophthalmoplegia; however, cranial nerves V and VII were intact. A bruit was not detected. Ophthalmoscopic examination revealed a pale-appearing retina with multiple horizontal striae, and "box-carring" of the arterial circulation of the retina with multiple flame-shaped hemorrhages scattered throughout (Fig. 2). The left eye was normal.

Invasion of orbital bones was not observed in the orbital x-rays and tomograms. However, computed tomography showed massive involvement of the or-



Fig. 1 (Perlman and McMahon). Proptosis of the right eye is noted with the blepharoptic eyelid resting on the chemotic and hemorrhagic conjunctiva. The orbital mass is most distinctly observed through the lateral aspect of the lower eyelid where a hard mass was palpated.

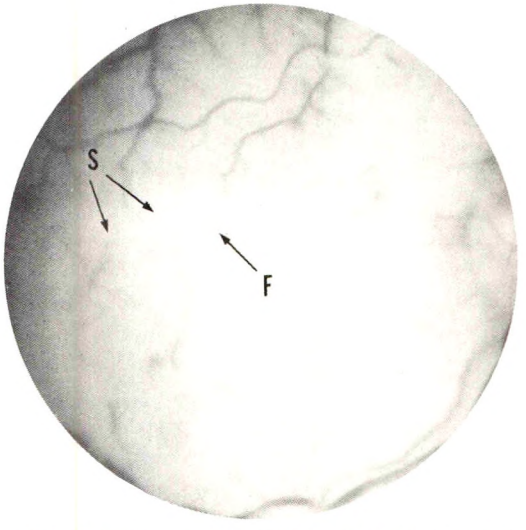


Fig. 2 (Perlman and McMahon). Central retinal artery occlusion. The retina is edematous with a slightly darker localized spot in the fovea (F). The arteries are incompletely observed because of decreased blood flow and edema of overlying retina. Multiple horizontal retinal striae course across the macula (S).

From the Department of Ophthalmology and Visual Science, Yale University School of Medicine, New Haven, Connecticut.

Reprint requests to Robert T. McMahon, M.D., 2710 Hospital Dr., Victoria, TX 77901.

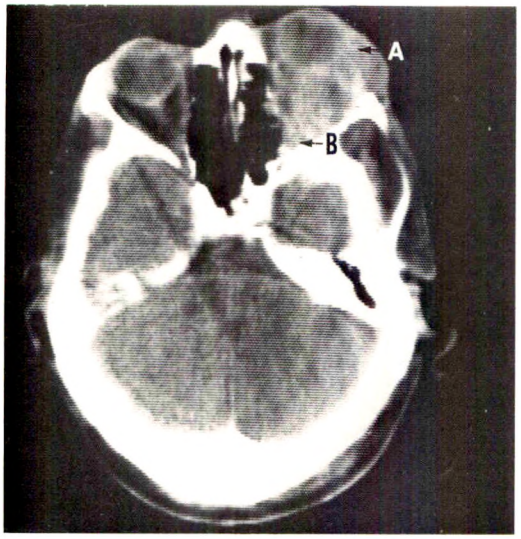


Fig. 3 (Perlman and McMahon). Computed tomography of the right orbit. Lateral aspect of eyelids and anterior orbit are infiltrated by tumor (A). Orbital apex contains posterior extension of tumor. Tumor mass indicates variable density (B).

bit extending from eyelids to optic foramen (Fig. 3). A somewhat homogeneous lesion was visible inferior to the globe. However, there was a marked variation in tumor density within the orbital apex. Both the sinuses and the orbital bones surrounding the orbit were normal.

A complete blood cell count showed a moderate macrocytic normochromic anemia caused by pernicious anemia. Evidence of metastatic lesions was not observed on chest x-rays, liver tests, liver-spleen scan, and bone scan.

Biopsy of a palpable lesion through the lateral aspect of the right lower eyelid was done on Oct. 26, 1977, and a diagnosis of sebaceous gland carcinoma was made. Because of the patient's good health and lack of evidence of metastatic disease, the right orbit was surgically removed on Nov. 8, 1977. A frozen section was then performed in the region of the optic foramen and malignant cells were identified.

The postoperative period was uneventful, and radiotherapy localized to the right orbit was begun several weeks after the procedure. The patient died Feb. 15, 1977, and a postmortem examination was refused.

Results

The specimen measured 37 × 37 × 36 mm and included the eyelids attached anteriorly (Fig. 4). The globe was displaced superiorly by this orbital mass. Multiple localized lesions were observed at the posterior margin of the specimen.

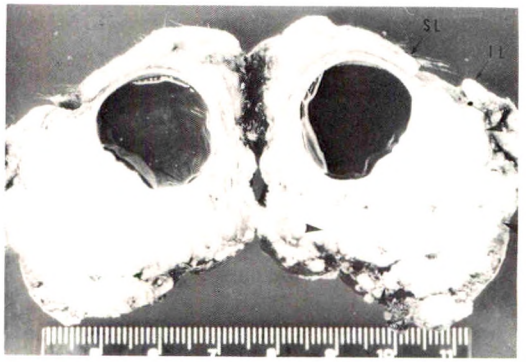


Fig. 4 (Perlman and McMahon). Gross examination of specimen (verticle section). Superior (SL) and inferior (IL) eyelids are noted anteriorly. Globe is displaced superiorly by inferior part of tumor mass. (Tumor mass is outlined by single arrows.)

The biopsy specimen obtained from the inferolateral aspect of the right eyelid showed normal sebaceous cells transforming into frank malignant cells (Fig. 5, top). The cytoplasm of normal sebaceous cells was milky in color. The nucleus was distinctly basophilic, minute in size, and centrally located. The point of transformation into anaplastic cells showed variation in both size and staining characteristics of nucleus and cytoplasm. The nucleus in these carcinomatous cells enlarged and became vesicular in appearance. The cytoplasm of most of these neoplastic cells was vacuolated (Fig. 5, bottom). Lipid stains such as oil red-0 confirmed the production of lipid products contained within these vacuoles. Less differentiated cells, which did not produce lipid, were also evident adjacent to lipid-containing cells (Fig. 6). Necrosis of tumor cells produced centrally located pyknotic and fragmented nuclei mixed with inflammatory cells. Differentiated cells in the periphery of this nodule were producing lipid within cytoplasmic vacuoles.

The retina was also affected by this underlying orbital process. Both the ganglion and the glial cells of the ganglion cell layer were almost totally absent, with

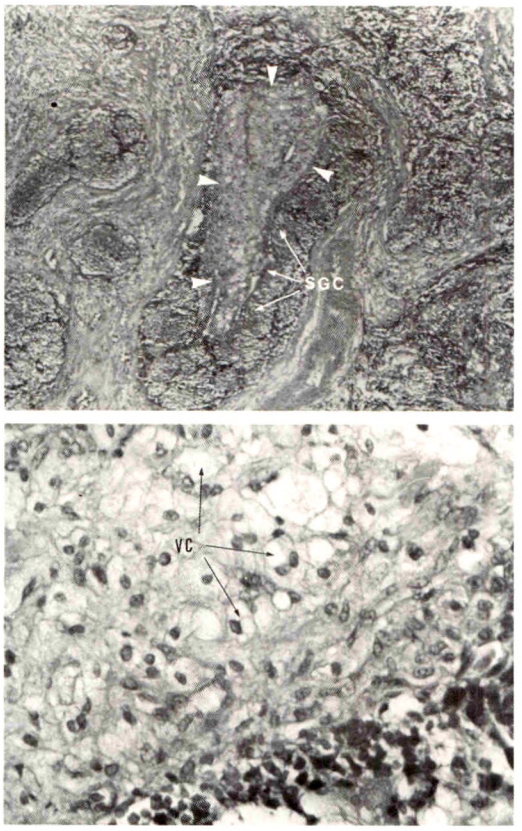


Fig. 5 (Perlman and McMahon). Sebaceous gland carcinoma. Top, normal sebaceous gland outlined by single arrows. Transformation of benign sebaceous cells into sebaceous gland carcinoma (SGC) at edge of normal sebaceous gland. Bottom, Malignant cells have larger nuclei with vacuoles in cytoplasm (VC), which contain lipid-containing material (top, ×31; bottom, ×130).

only a few pyknotic nuclei remaining (Fig. 7). The inner nuclear layer was diminished in size and contained numerous pyknotic nuclei. Extracellular edema was also observed in both the nerve fiber and external plexiform layers.

Discussion

Sebaceous gland carcinoma is most commonly an isolated, painless nodule.[2] In most cases with eyelid swelling, the diagnosis of chalazion is made.[3] However, yellowish discoloration of the lesion should alert the clinician to the possibility of sebaceous gland carcinoma. Blepharitis and conjunctivitis are two other incorrect diagnoses that are made in cases with sebaceous gland carcinoma. Pagetoid invasion of the epithelium of the eyelid or conjunctiva produces these two clinical appearances.[3] Complete excision of the tumors with diffuse superficial spread is possible only with more extensive procedures.[4]

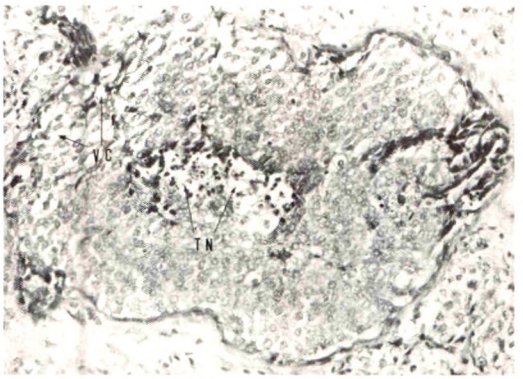


Fig. 6 (Perlman and McMahon). Sebaceous gland carcinoma. Tumor nodule is primarily composed of immature cells with vesicular nuclei. A central focus of tumor necrosis (TN) is noted with pyknotic nuclei and nuclear debris mixed with a few acute inflammatory cells. The periphery of this nodule contains lipid cells (VC) (×81).



Fig. 7 (Perlman and McMahon). Retina in macular region. Ganglion cell and nerve fiber layer are edematous (GCL). Ganglion and glial cells are decreased in number. Cells in inner nuclear layer (INL) are numerically diminished. Some of the remaining nuclei are variably pyknotic. Marked extracellular edema (EPL) separates fibers of this layer (×104).

Straatsma[3] found an average period of three years that elapsed between the initial recognition of eyelid swelling and correct diagnosis in these lesions. This long period of delay in making a correct diagnosis adversely affects the prognosis in this particular tumor.

The average age that these lesions appear is 61.6 years.[1] At 82 years of age, our patient represents one of the oldest cases reported. In contrast to basal cell carcinoma, sebaceous gland carcinoma most commonly affects the upper eyelid. Although the exact origin is sometimes difficult to determine because of generalized involvement of the eyelid, Boniuk and Zimmerman[1] found the meibomian glands to be the most common point of origin.

Our patient had an initial history of proptosis. The patient denied the presence of isolated eyelid mass during the course of his disease. Absence of a history of eyelid nodule is unusual for this type of tumor. The eyelid margins and eyelashes were also unaffected, both by clinical and histologic examination.

Secondary involvement of orbital structures can occur in patients with space occupying lesions of the orbit. The presence of an afferent pupillary defect, as was present in our case, usually indicates that the optic nerve has been damaged. However, our patient had the ophthalmoscopic appearance of a central retinal artery occlusion, which could explain the pupillary abnormality.

Venous stasis is a well-recognized clinical finding with orbital leisons. However, the clinical picture of central retinal artery occlusion has never been reported associated with a constrictive orbital lesion. The chance that the vascular accident was unrelated to the basic pathology must also be considered.

The computed tomography diverted us from the diagnosis of sebaceous gland carcinoma, because posterior extension to the optic foramen by this lesion was thought to be highly unlikely for this particular tumor. The variation in tumor density in computed tomography was also an interesting finding. Large areas of necrosis of sebaceous gland carcinoma, which were enclosed by viable tumor, produced this variation in density.

A biopsy was performed after removal was complete. Material from the optic foramen indicated malignant cells. The remaining tumor was treated with radiotherapy. Although sebaceous gland carcinoma is believed to be radioresistant, others think that tumor regression is possible with this modality.[2,5]

The pathologic diagnosis of sebaceous gland carcinoma can be difficult. Boniuk and Zimmerman[1] found the correct diagnosis in only 35 of 70 cases by contributing pathologists. The two most common pathologic misdiagnoses made are basal cell and squamous cell carcinomas. However, the correct diagnosis can be made when lipid material is recognized within the cytoplasm of these cells. If the clinician suspects the possibility of sebaceous gland carcinomas, a frozen section of formalin-fixed tissue stained with oil red-0 will confirm the diagnosis. Dehydration with alcohol should not be used because extraction of lipid material will occur. Tumor cells originating from the normal sebaceous gland are also a valuable indicator of sebaceous gland carcinoma.

The pathologist should also be aware that basal cell carcinoma,[6,7] and rarely lacrimal gland tumors, may show sebaceous differentiation. However, the characteristic cells present in these tumors are evident with a thorough microscopic examination.

SUMMARY

We diagnosed sebaceous gland carcinoma of the right lower eyelid in an 82-year-old man. Computed tomography

showed the lesion extending from the eyelids anteriorly to the optic foramen posteriorly. With this orbital neoplasm, was an occlusion of the central retinal artery in his right eye. The right orbit was removed surgically and biopsy of the optic foramen region indicated malignant cells. Localized radiation to the right orbit was then initiated postoperatively.

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OPHTHALMIC MINIATURE

For a week now there has been a foreigner in the Salpêtrière, a definitely Germanic type and yet somehow different; I can't quite make him out. Wednesday is the day we go to the ophthalmological room, and there this foreigner suddenly began behaving with some authority; when he exchanged cards with Charcot's ophthalmologist, the latter became very polite and expressed the hope that Monsieur would often return so that he could learn something from him. Whereupon we all began wondering who he might be. Before leaving he came over to us Viennese and said: "I heard you speaking German. I'd like to introduce myself." My bête noire exchanged cards with him first and I was still trying to find mine when the foreigner said: "I am a German, but I emigrated to America long ago." At last I gave him my card, but it happened to be one without an address. He glanced at it and said: "Could you be Dr. F. from Vienna? I've known your name for a long time, from your publications, especially the one on cocaine." I was a little surprised and inquired after his name, which turned out to be Knapp. Now, Knapp is the foremost ophthalmologist in New York, who has also written a lot about cocaine and to whom I once wrote a letter in Koller's name. I greeted him accordingly and my bête noire stood there looking rather sheepish, first of all because he had failed to recognize the man, and second because he had again managed to make a fool of himself. When he heard the word cocaine mentioned he asked: "Have you also written about cocaine?" Whereupon Knapp replied: "Of course he has, it was he who started it all." This morning my Viennese was much more malleable and talked exclusively of the great practice that awaited me in Vienna . . .

Sigmund Freud, *Cocaine Papers*
Edited by Robert Byck
New York, New American Library, 1974

MICROSURGICAL REMOVAL OF A PRIMARY INTRAORBITAL MENINGIOMA

LOUIS E. MARK, M.D., JOHN S. KENNERDELL, M.D., JOSEPH C. MAROON, M.D., ARTHUR E. ROSENBAUM, M.D., RALPH HEINZ, M.D., AND BRUCE L. JOHNSON, M.D.

Pittsburgh, Pennsylvania

The well-known prognosis for meningiomas of the orbit or cranio-orbital junction is visual loss. We recently removed a primary intraorbital optic nerve sheath meningioma in a patient whose visual acuity was finger counting for about six months. Although the tumor encircled the nerve, only mild optic atrophy was present. Postoperatively, visual recovery was almost complete, which was undoubtedly related to a fine balance having been maintained between the compressive force of the tumor and the vascular supply to the nerve. To our knowledge, this is the first report of visual recovery following microsurgical orbital dissection for this type of tumor.

CASE REPORT

A 48-year-old woman in good health was referred to the Pittsburgh Eye and Ear Hospital in October 1977 because of poor vision in her left eye. Three years earlier her visual acuity in that eye had been 6/6 (20/20) with correction as documented by her optometrist, but when she returned to him in February 1977, it was 6/60 (20/200). Shortly after this visit, the patient reported that her vision had decreased even more. In August her vision was measured at finger counting, and she was referred to an ophthalmologist. Routine skull and orbital x-ray films were normal. Treatment with a tapering dose of oral prednisone for suspected retrobulbar neuritis was instituted and continued for one month without improvement of vision. A computed tomography scan then revealed a left retrobulbar enhancing mass lesion (Fig. 1, left).

Our examination of the patient revealed an uncorrected visual acuity of R.E.: 6/4.5 (20/15); L.E.: finger counting at one foot. Color vision was normal in the right and absent in the left eye. The left pupil displayed a 4+ Marcus Gunn reaction. Extraocular movements were full and conjugate. Hertel exophthalmometry revealed 2 mm of proptosis on the left side with a definite resistance to retropulsion of the left globe. There were no orbital bruits and the slit-lamp examination and tonometric readings were normal bilaterally. The left disk showed only mild temporal optic atrophy; there were no optociliary shunt vessels, or retinal striae or disk edema. The right fundus was normal. The left visual field showed a deep inferior altitudinal depression (Fig. 2, left). Contact A- and B-scans confirmed the presence of a large, solid, rounded mass intimately connected to the optic nerve (Fig. 3). Pluridirectional tomography (Polytomes) of the optic canals was normal. The patient was admitted on a presumptive diagnosis of an optic nerve meningioma. This diagnosis was further substantiated by selective carotid angiography, which showed a 1.5-cm minimally vascular, spherical retrobulbar tumor (Fig. 4).

After informed consent was obtained, the patient underwent a modified Kronlein lateral orbitotomy on Nov. 9, 1977. Exposure obtained by means of a modified DeMartel-Weitlaner orbital retractor allowed the dissection to be carried down to the tumor. The optic nerve was surrounded by a partially encapsulated mass forming an incomplete ring opened medially (Fig. 5). A frozen section of the tumor was reported as meningioma. A plane between tumor and nerve was found, and the tumor was excised in toto by means of microsurgical technique using long handled angulated instruments and bipolar cautery (Fig. 6, left). During the dissection, we paid special attention to the preservation of the vascular supply to the optic nerve.

The histopathologic examination of the specimen revealed a typical meningothelial meningioma (Fig. 6, right). No dural tissue could be identified on multiple cut sections.

Postoperative orbital swelling was minimized by therapy with oral prednisone. Unexpectedly, the visual acuity in the left eye was 6/18 (20/60) one day after surgery, improving to 6/9 (20/30) on the second postoperative day. The visual field became full, leaving only a slight enlargement of the blind spot (Fig. 2, right). The patient was discharged on the third postoperative day. Two months later, visual acuity was 6/7.5 (20/25) without correction, and color perception had returned fully. The minimal

From the Departments of Ophthalmology (Drs. Mark and Kennerdell); Neurology (Dr. Kennerdell); Neurosurgery (Dr. Maroon); Radiology, Division of Neuroradiology (Drs. Rosenbaum and Heinz); and Pathology, Division of Neuro- and Ophthalmic Pathology (Dr. Johnson), the University of Pittsburgh, Pittsburgh, Pennsylvania. This study was presented in part at the Neuro-Ophthalmologic Pathology Symposium at the Wilmer Ophthalmological Institute, Johns Hopkins University, Baltimore, Maryland, Feb. 11, 1978.

Reprint requests to John S. Kennerdell, M.D., Eye and Ear Hospital, 230 Lothrop St., Pittsburgh, PA 15213.

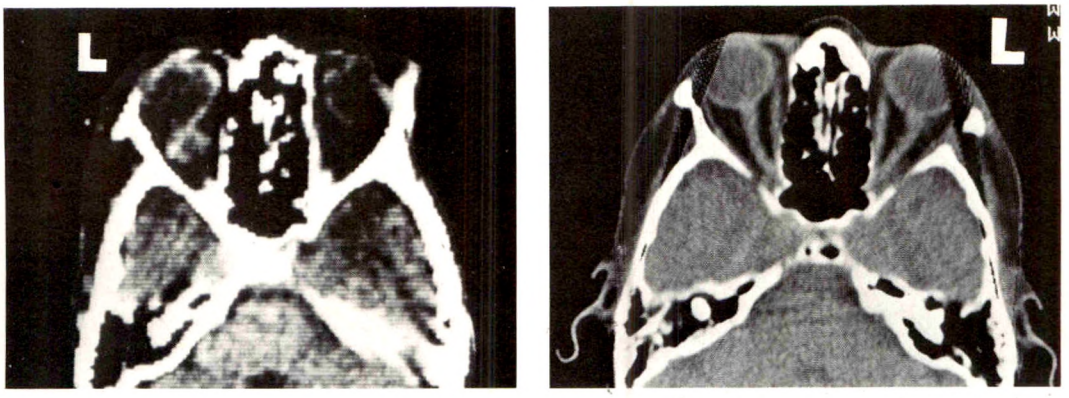


Fig. 1 (Mark and associates). Left, Preoperative computed tomography scan showing globular mass in region of optic nerve behind left globe. Right, Postoperative scan demonstrating essentially normal left optic nerve shadow and mild postinflammatory orbital reaction. Note reversal of the two images.

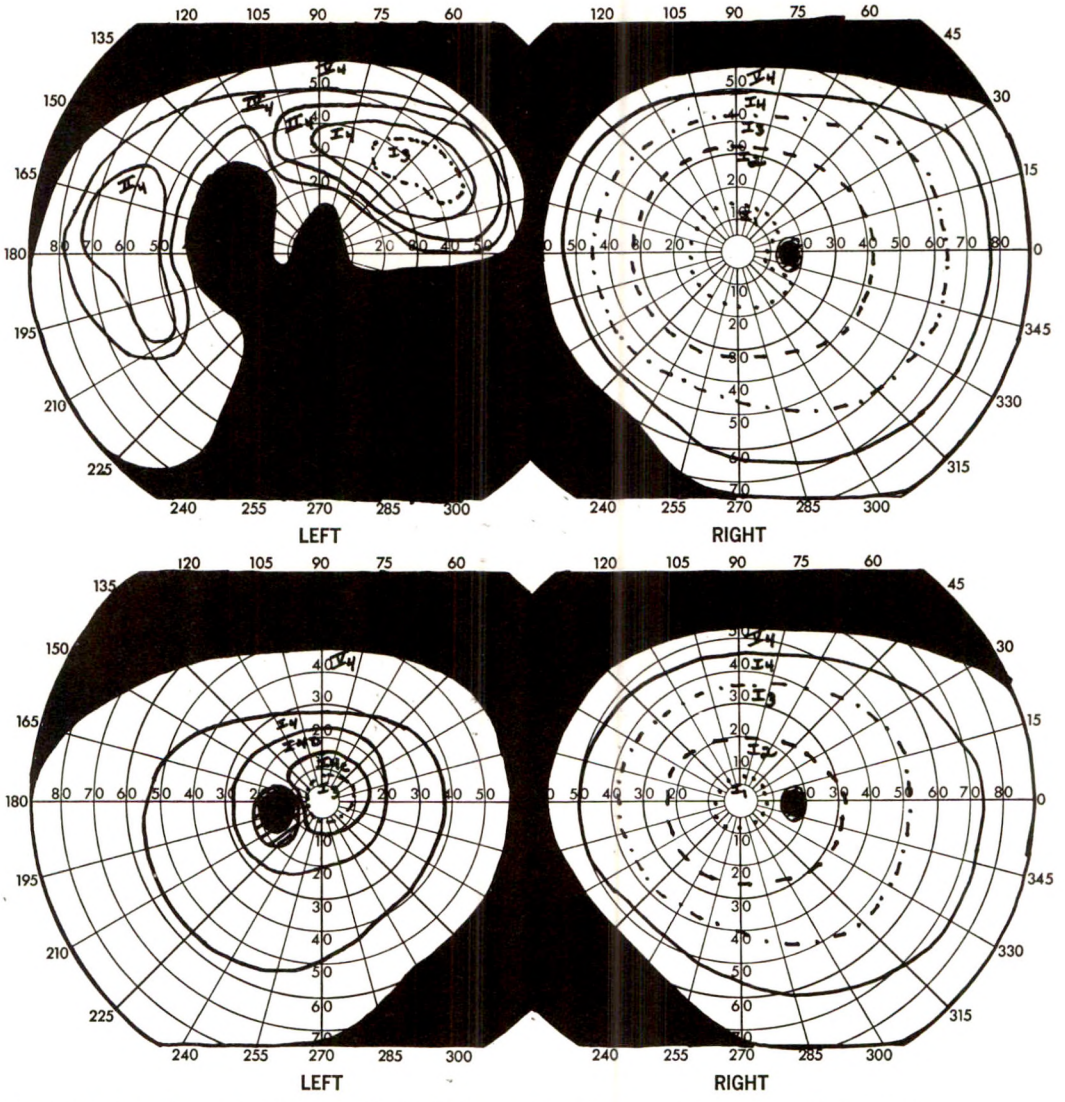


Fig. 2 (Mark and associates). Visual field of left eye. Top, Preoperative. Bottom, Postoperative.

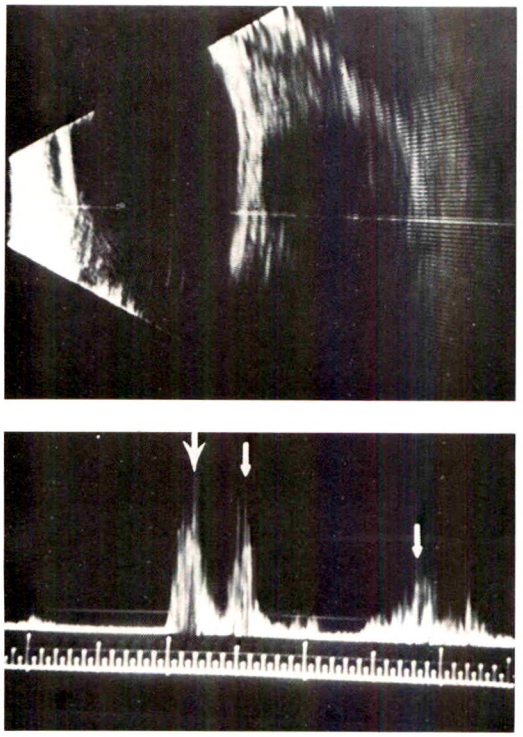


Fig. 3 (Mark and associates). Top, Ultrascan B-scan demonstrating a round mass in the anterior midorbit behind the globe in the area of the optic nerve. The acoustical consistency is variable and the acoustical beam is significantly attenuated. Bottom, Ultrascan A-scan showing the mass behind the globe. The large arrow indicates the posterior wall of the globe, and the smaller arrows indicate the anterior and posterior walls of the tumor. Some small echoes in the tumor demonstrate variation in the acoustical texture, whereas smaller posterior wall echoes demonstrate acoustical attenuation.

proptosis had resolved. The pupil now demonstrated only a 1 + Marcus Gunn reaction; the disk was unchanged in appearance. A computed tomography scan three months after surgery showed the optic nerve (Fig. 1, right) to be normal in size and configuration on basal and coronal views. Five months after surgery the patient's visual acuity in her left eye was 6/6 (20/20).

Discussion

Primary intraorbital optic nerve sheath meningiomas frequently cause devastating visual loss. This happens either by nerve compression with resultant atrophy or as a sequela of the surgical attempt to extirpate the tumor. Survival is good because such tumors do not metastasize and being confined to the orbit, they are accessible for complete removal. Incomplete tumor excision allows for recurrence and intracranial extension through the optic canal.

No general consensus exists as to how best to treat adult patients with primary optic nerve meningiomas. Most of these tumors are likely to extend intracranially; thus, Newell and Beaman[1] suggested that they should be removed by a neurosurgeon capable of unroofing the orbit and canal. Henderson[2] advised resection of extradural, globular, and small anteriorly placed tumors by the lateral orbital approach; most tumors are otherwise best handled by resection of the nerve between the eye and the optic foramen from above (unilateral blindness being preferred to tumor recurrence). Jakobiec and Jones[3] concurred with an en bloc excision

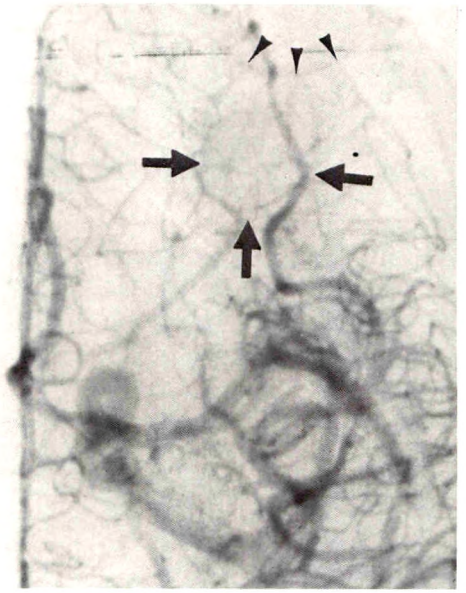


Fig. 4 (Mark and associates). Base view of selective left internal carotid angiogram (intermediate phase). Note circular blush (large arrows) of tumor located directly behind globe, demarcated by choroidal blush (small darts). The blush begins in the arterial phase, persists through the intermediate and late venous phases, and is typical of meningiomas.

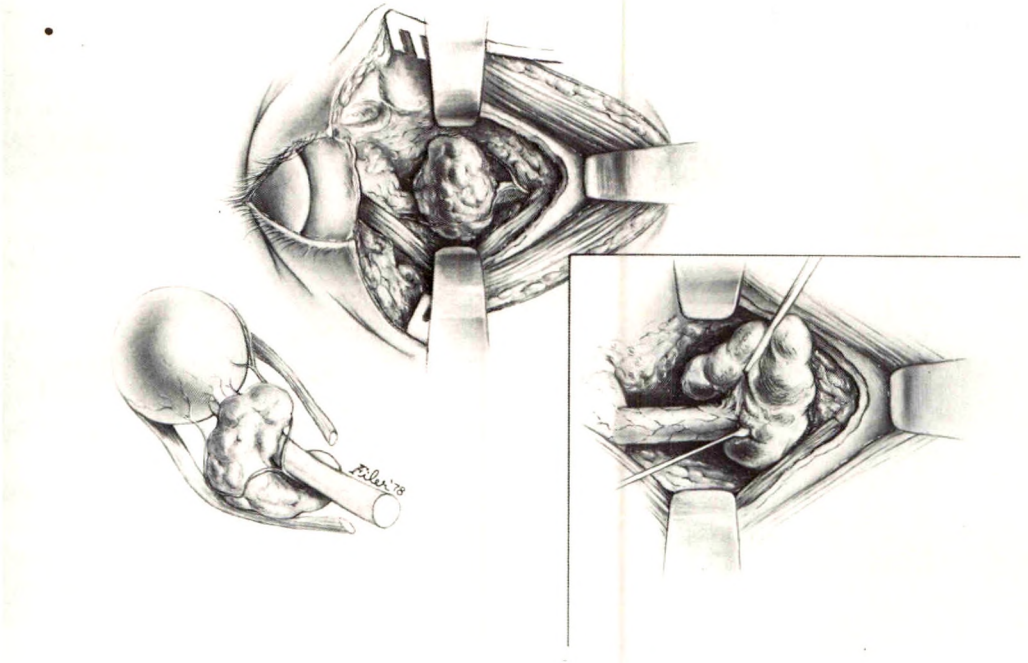


Fig. 5 (Mark and associates). Artist's recreation of in situ tumor and microsurgical dissection.

of the optic nerve, but admitted that rarely a tumor can be peeled off from the nerve with retention of useful vision. Conversely, Wright[4] and Walsh,[5] noting that meningiomas are slow-growing tumors, recommended a conservative, nonsurgical approach to the problem. Other reports[6,7] described the sacrifice of both the globe and the nerve or the nerve alone, often in the presence of good vision. Tumorous invasion of the globe or monstrous orbital enlargement sometimes requires enucleation or exenteration.[1,8–10] Smith[11] urged radiation to treat intracanalicular meningiomas, but did not mention whether this form of therapy is applicable to meningiomas confined to the orbit.

Encasing nerve sheath meningiomas cannot be excised without irreparably damaging the vascular supply to the nerve. As described by Wright[4] and Walsh,[5] these tumors arise from arachnoidal tissue. Their initial confinement by the dura is what causes them to compress the optic nerve and compromise vision; the unique arrangement of perforating dural vessels and connective tissue septa unites the meninges and nerve into an integral, almost inviolable anatomical unit. Sometimes, however, early extradural extension of the tumor may spare the nerve from strangulation. Similarly, as Henderson and Campbell[10] pointed out, the tumor may rarely originate from ectopic rests of arachnoid cells along some of the nerves in the reticular tissue of the orbit. In both situations, the tumor may grow around the nerve extradurally and either rob or spare the patient's sight. Als[7] reported the case of a 24-year-old man with 3 mm of proptosis and visual acuity

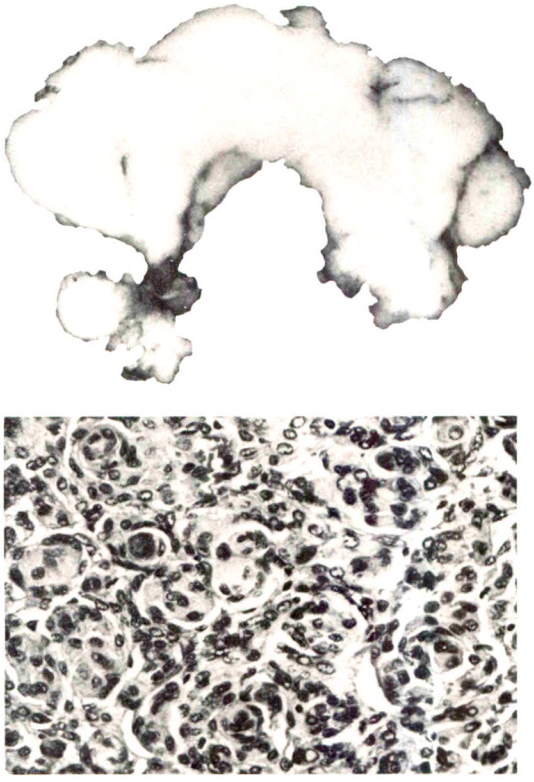


Fig. 6 (Mark and associates). Top, Excised tumor demonstrating notch from optic nerve. Bottom, Histologic section of meningothelial meningioma.

of 6/6 (20/20) in each eye who underwent a transcranial radical resection of his right optic nerve and surrounding meningioma. Postoperative examination of the specimen revealed a distinct cleavage plane between the tumor and nerve throughout its length and no tumor infiltration of the nerve itself. The author concluded that "radical removal with sparing of the optic nerve would probably have been technically feasible if attempted."

Conversely, meningiomas that extend beneath the dura of the optic nerve sheath do not inevitably compress the nerve or cause significant visual loss in all cases.[12] Therefore, unless exploratory surgery is undertaken, the true nature of the tumor and its relationship to the dural sheath and nerve cannot be ascertained accurately. We agree that most patients found to have orbital optic nerve tumors consistent with meningiomas on the basis of computed tomography scan and comprehensive ultrasonography will have progressive visual loss and optic atrophy because of intradural growth. We suggest, however, that such patients whose cases are diagnosed before they develop significant optic atrophy or chronic disk edema with shunt vessels undergo exploratory surgery on the chance that the tumor is resectable, either because it has left the vaginal space early or because its origin is extradural.

We chose to operate on our patient for several reasons. First, we believed that total blindness in the affected eye was certain to occur because of her already poor visual acuity of such long duration. Secondly, the nerve head was only minimally pale and there were no optociliary shunt vessels to suggest the poor prognosis found by Hollenhorst, Hollenhorst, and MacCarty[13] when such vessels are seen. Third, although confined to the anterior orbit, the tumor had the potential to grow intracranially; complete removal might have effected a cure. Lastly, we felt confident in our microsurgical approach to the orbit.[14,15]

Although dural tissue could not be identified histopathologically, suggesting that this tumor arose outside the sheath, purely etopic meningiomas are rare. Of 25 primary intraorbital meningiomas studied by Karp and associates,[16] not one tumor of this kind was found. Because of this, we acknowledge the possible fortuitous nature of our case. We plan to observe our patient closely.

Summary

A 48-year-old woman with a primary intraorbital meningioma associated with the optic nerve sheath underwent a micro-

surgical removal of the tumor through a lateral orbitotomy. Visual recovery was essentially complete.

ACKNOWLEDGMENT

Martin Winkler, M.D., referred the patient.

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BILATERAL NECROTIZING SCLERITIS

TAKA-AKI HATSUDA, M.D., AND JUNICHI TANAKA, M.D.

Kyoto, Japan

Necrotizing inflammation of the sclera is a rare, severely destructive condition that sometimes leads to the loss of an eye after deteriorating vision and severe pain. The essential pathologic change consists of a central area of necrosis surrounded by a palisade of epithelioid and giant cells, which is most clearly seen in a subcutaneous rheumatic nodule. There are four distinctive clinical entities that can be ascribed to the collagen diseases, particularly to rheumatoid arthritis: episcleral rheumatic nodules, scleromalacia perforans, necrotizing nodular scleritis, and massive granuloma of the sclera.[1,2] We described herein a case of bilateral necrotizing scleritis, necrotizing nodular scleritis in the left eye and massive granuloma of the sclera in the right, observed in a woman whose history was noncontributory for rheumatoid arthritis or collagen disease.

CASE REPORT

A 53-year-old woman first came to our clinic in November 1974 complaining of painful red eyes with progressive loss of vision over the past several months.

The ophthalmologic examination on Nov. 30 revealed visual acuity of R.E.: 6/15 (20/50); L.E.: 6/120 (20/400). The eyes were deeply injected, especially in the left eye. Slit-lamp examination of the left eye showed a cloudy cornea, fine keratic precipitates, flare and cells in the anterior chamber, almost complete posterior synechiae, and hazy media. The pupil was fixed and irregular. The right eye was similar to the left eye except for a transparent cornea, less posterior synechiae, and little haze in the media. The pupil could not be well dilated. Gonioscopy revealed open angles. The fundus of the left eye was invisible. The right fundus had a hyperemic disk, but was otherwise normal. Intraocular pressure was R.E.: 12 mm Hg; L.E.: 27 mm Hg.

The physical examination revealed no other significant abnormalities. Routine laboratory studies including a complete blood cell count, platelets, erythrocyte sedimentation rate, urinalysis, electrolytes, lupus erythematosus preparation, an antinuclear antibody titer, and a serologic test for syphilis gave normal results.

The patient's history, repeated physical examination, and laboratory studies revealed no arthritis or collagen disease.

A diagonosis of bilateral iridocyclitis was made. The eyes were treated with atropine and local and systemic corticosteroids. The eye disease showed several remissions and exacerbations during the following several months. In September 1975, the left eye became progressively injected and painful despite vigorous treatment. In the beginning of November, a nodular lesion appeared on the scleral surface from 4 to 8 mm posterior to the corneoscleral limbus, at the 11 o'clock position. The visual acuity decreased to light perception. One week later a dark spot was discovered at the top of the lesion. At the end of the next week, a yellow center of necrosis developed in the nodule. Neighboring insertion of the superior rectus muscle and overlying conjunctiva became necrotic (Fig. 1). The visual acuity had decreased to no light perception, and intraocular pressure was 4 to 7 mm Hg. Because of intolerable pain in this blind eye, the eye was removed Dec. 1, 1975. No implant was used following the enuclea-

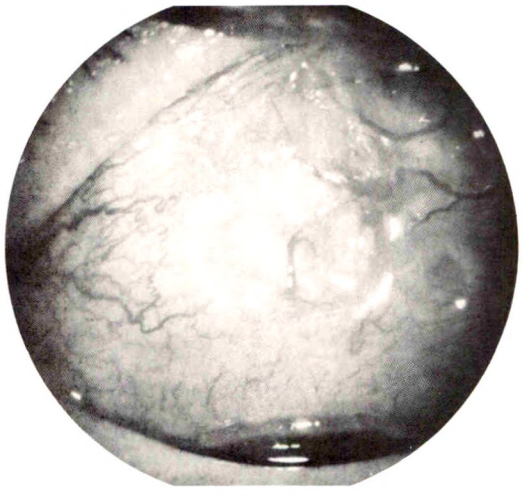


Fig. 1 (Hatsuda and Tanaka). Left eye with necrotizing nodular scleritis.

From the Departments of Ophthalmology (Dr. Hatsuda) and Pathology (Dr. Tanaka), Kyoto Prefectural University of Medicine, Kawaramachi, Kyoto, Japan.

Reprint requests to Taka-aki Hatsuda, M.D., Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kawaramachi, Kyoto 602, Japan.

tion because of widespread necrosis of the conjunctiva and Tenon's capsule. The pain had disappeared after the enucleation. The socket healed nicely and a prosthesis was tolerable.

The right eye had been relatively quiet except for several episodes of iridocyclitis. The visual acuity of the eye was 6/60 (20/200), on Jan. 12, 1976. The right eye had the first episode of scleritis Jan. 16, 1976. Scleritis was situated nasally, appeared to be deep, and extended from the corneoscleral limbus to the insertion of the medial rectus muscle. Moderate flare and cells were present in the anterior chamber. Intraocular pressure was 5 mm Hg. Increasing cataract and medial haze obscured the fundus. The visual acuity had decreased to finger counting. The eye was treated mainly with indomethacin suppositories and supplementarily with retrobulbar or systemic corticosteroids. After several remissions, bluish prominent lesions appeared at the insertion of the lateral rectus muscle and adjacent to the superior corneoscleral limbus in June 1976. The cornea became entirely edematous and was neovascularized around its circumference. The vision decreased to blindness. Three months later two necrotic foci appeared, one superior to the insertion of the lateral rectus muscle and the other just lateral to the insertion of the superior rectus muscle. The necrotic lesions grew and fused together (Fig. 2). The ocular disease rapidly progressed, with recurrent severe pain and increasing pericorneal injection. The eye exhibited extreme limitation of movement in all directions. The pain was intolerable, and the patient was anxious to have the eye removed. The eye was enucleated on Nov. 22, 1976. During surgery, a dense cartilage-like mass was found adherent to the globe and to the loose tissues of the orbit in an equatorial portion nasosuperiorly. The mass seemed to be an extension of inflammatory infiltrates into the loose tissue of the orbit. No implant was used after the enucleation because the indurated ocular socket would not tolerate it.

A dull pain persisted after enucleation. One week postoperatively, the patient began having a sharp pain in her right ocular socket. Examination showed a hard and tender mass occupying the socket. We found a rapidly enlarged mass filling the empty socket. Because of increasing pain, the orbital mass was removed Jan. 10, 1977. The pain disappeared after the surgery.

The patient had no symptoms of arthritis or any other general disease at her last examination July 2, 1977.

Results

Immediately after enucleation, the globes were fixed in 10% formalin solution and embedded in paraffin blocks.

The left eye was of normal size (Fig. 3). The cornea was normal. The sclera superior to the corneoscleral limbus surrounding the nodular lesion was three times the normal thickness, and the thickening extended to the equator. There was a large area of exudative retinal detachment. High-power microscopic examination of the thickened lesion revealed that it consisted of a massive chronic inflammatory process, which had some of the characteristics of a granulomatous inflammation. The lesion was composed of a central focus of necrosis surrounded by densely arranged lymphocytes, epithelioid cells, and multinucleated giant cells in some areas (Fig. 4). Extensive interruption and necrosis were observed in the scleral collagen bundles. To a lesser extent, a simi-

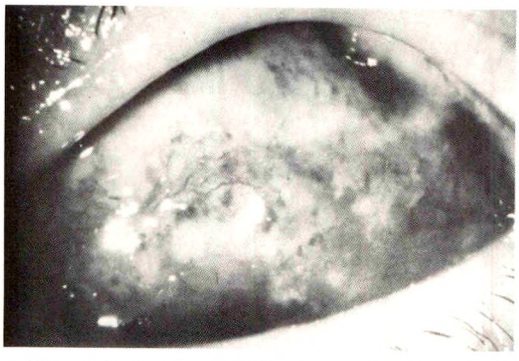


Fig. 2 (Hatsuda and Tanaka). Right eye with extensive necrotizing nodular scleritis.



Fig. 3 (Hatsuda and Tanaka). Left eye. Low-power view of equatorial section. Sclereal thickening extends superiorly from corneoscleral limbus to equator. Retina is detached with eosinophilic subretinal fluid. Lens has been removed before parrafin embedding (hematoxylin and eosin, ×2).

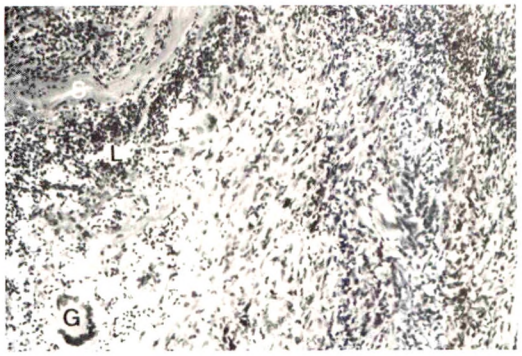


Fig. 4 (Hatsuda and Tanaka). Left eye. High-power view of scleral granulomatous lesion. (L) Dense lymphocytic infiltration, (E) palisading arrangement of epithelioid cells, (S) interrupted bundles of scleral collagen, (G) multinucleated giant cell (hematoxylin and eosin, ×190).

lar process was discernible in the inferior sclera. The sclera posterior to the equator was involved, as evidenced by some focal collection of lymphocytes.

Iris, ciliary body, and choroid involved in the area of the scleral granuloma showed a diffuse infiltration with lymphocytes and epithelioid cells. Some of the epithelioid cells contained pigment granules in the cytoplasm. Remaining portions of the choroid showed only diffuse infiltration of lymphocytes. The retina was completely detached, contained eosinophilic subretinal fluid, and was mildly involved in the inflammatory process. The pigment epithelium was destroyed in the area of scleral granuloma. The optic nerve was somewhat atrophic and associated with slight gliosis.

The right eye was phthitic. The cornea was involved with superficial and midstromal neovascularization and perivascular lymphocytic infiltration, most marked at the corneoscleral limbus (Fig. 5). The sclera had extensive thickening and formed a tumor-like mass that occupied the vitreous cavity. High-power microscopic examination of the mass revealed it to be composed of loose scar tissue with massive lymphocytic infiltration, in which epithelioid cells and occasional giant cells were scattered (Fig. 6). Most of the collagen bundles of the sclera were distorted and necrotic. There was little vascularized infiltration in the sclera.

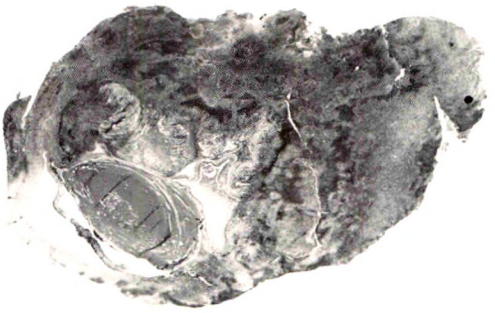


Fig. 5 (Hatsuda and Tanaka). Right eye. Low-power view of section of whole eye. Granulamatous mass occupied vitreous cavity. Episclera and choroid are markedly involved by inflammatory process (hematoxylin and eosin, ×2).

Iris, ciliary body, and choroid were disintegrated and diffusely infiltrated by lymphocytes and scattered epithelioid cells. Occasional phagocytosis of pigment granules occurred in the epithelioid and giant cells (Fig. 7). The retina was atrophic. The optic nerve was also atrophic and gliotic.

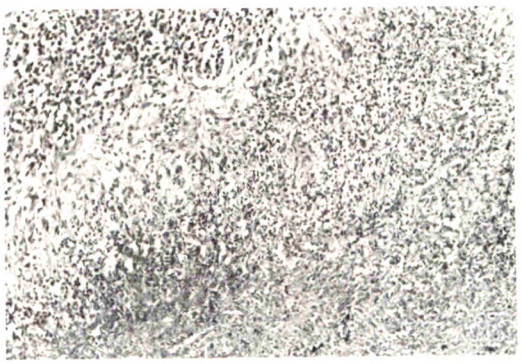


Fig. 6 (Hatsuda and Tanaka). Right eye. High-power view of scleral granuloma. Scleral collagen bundles are distorted and almost missing. Massive lymphocytic infiltration and palisade arrangement of epithelioid cells are seen. No giant cells are present in this area. There is little vascularization (hematoxylin and eosin, ×190).

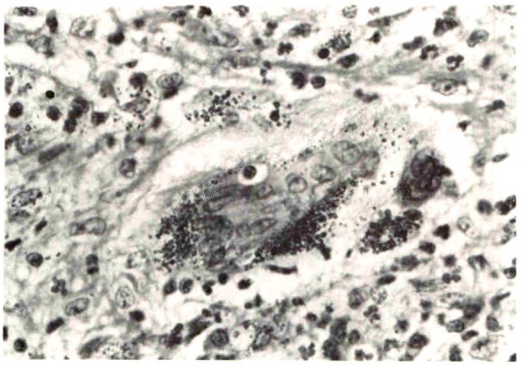


Fig. 7 (Hatsuda and Tanaka). Right eye. High-power view of scleral granuloma near ciliary body. Note epithelioid cells and giant cell containing pigment granules (hematoxylin and eosin, ×380).

The cartilage-like mass attached to the sclera and orbital adnexae was histologically confirmed to be composed of fibroadipose tissue markedly infiltrated by granuloma, indicating intraorbital involvement of the scleral lesion (Fig. 8).

Discussion

Necrotizing granulamatous scleritis is a rare ocular disease; necrotizing nodular scleritis, a violent inflammatory reaction usually associated with the somewhat loosely linked group of collagen diseases, particularly rheumatoid arthritis, is even rarer. The characteristic histologic appearance of nodular granulomatous scleritis is a central area of necrosis surrounded by a palisading zone of epithelioid and multinucleated giant cells, a granulomatous lesion most typically seen in a subcutaneous rheumatic nodule. The etiology of the condition is unknown.

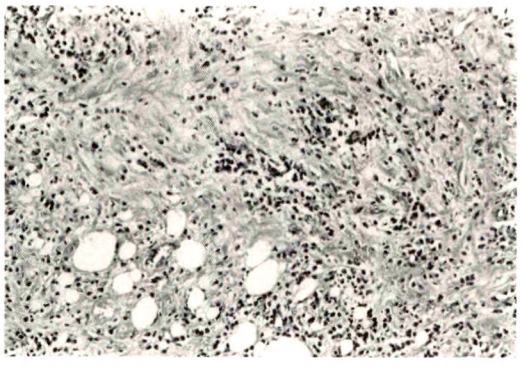


Fig. 8 (Hatsuda and Tanaka). High-power view of intraorbital mass developing among orbital adnexae after enucleation of right eye. It consists of fibroadipose tissue mainly involved by diffuse lymphocytic infiltration (hematoxylin and eosin, ×190).

In this case the pathologic findings were necrotizing nodular scleritis in the left eye and massive granuloma of the sclera in the right eye. Scleral lesions of both eyes began with nodular scleritis, which developed necrosis resembling scleromalacia perforans, but with violent inflammatory symptoms. This strongly suggests that massive granuloma of the sclera is the severe condition of necrotizing granulomatous scleritis. Wolter and Bentley, [2] who reported two cases of a combination of scleromalacia perforans and massive granuloma of the sclera, stated that differences in the degree of necrosis and scar formation as well as location in the sclera distinguished three conditions: scleromalacia perforans, necrotizing nodular scleritis, and massive granuloma of the sclera.

Distinguishing between the three conditions by their histologic features is difficult. Franceschetti and Bischler[3] suggested that the term "scleromalacia perforans" be reserved for cases showing indolent necrotic sloughing and a quiet clinical course associated with rheumatoid arthritis, and that the expression "necrotizing nodular scleritis" should be used to designate cases exhibiting a violent inflammatory process, generally not associated with rheumatoid arthritis. Several researchers[4–6] have supported this suggested differentiation between scleromalacia perforans and necrotizing nodular scleritis. Van der Hoeve,[7] who was the first to characterize this dramatic syndrome as a clinical entity and named it scleromalacia perforans, suggested that the cases he described might belong to

two categories. Our case had no history of rheumatoid arthritis or other collagen disease. One of us (T. H.) had encountered a case of scleromalacia perforans in a 37-year-old woman with rheumatoid arthritis of six years' duration, whose left eye developed four necrotic nodules, which were resolved in four months. Hogan and Zimmerman[8] did not distinguish between rheumatoid lesions occurring in the sclera with or without a history of rheumatoid arthritis or related disease because of similarity in the histologic features. There may be some exceptions, consisting of a combined occurrence of scleromalacia perforans and massive granuloma of the sclera, as in the cases reported by Wolter and Bentley.[2] However, from our own experience, we prefer to divide necrotizing granulomatous scleritis into scleromalacia perforans and necrotizing nodular scleritis.

Summary

A 53-year-old woman whose history was noncontributory for rheumatoid arthritis and collagen disease had bilateral necrotizing inflammation of the sclera. The left eye had necrotizing nodular scleritis and the right eye, massive granuloma of the sclera. In the right eye the orbital adnexae were also involved by granulomatous infiltration and developed a mass of fibroadipose tissue simulating an orbital tumor within a week after enucleation.

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LISTERIA MONOCYTOGENES ENDOPHTHALMITIS WITH A BLACK HYPOPYON

RICHARD L. ABBOTT, M.D., RICHARD K. FORSTER, M.D.,
AND
GERBERT REBELL, M.S.
Miami, Florida

Listeria monocytogenes is a gram-positive rod that is pathogenic most frequently in immunosuppressed persons or persons with altered defense mechanisms.[1] We describe herein the fourth known case of *L. monocytogenes* as a cause of endogenous endophthalmitis. Significantly, the three previously described patients were known to be in good health, and no extraocular septic foci were found in them. All of the patients had similar signs and symptoms and had poor vision despite therapy. Our case was unusual because of the presence of a pigmented hypopyon, which simulated a necrotic intraocular melanoma or tumor metastatic to the uvea.[2] We emphasize the importance of performing a diagnostic paracentesis for histopathology and culture in cases of this type so that appropriate therapy can be initiated promptly.

CASE REPORT

A 68-year-old healthy woman went to her local ophthalmologist and complained of a sudden onset of acute pain and decreased visual acuity in the right eye, preceded by a two-day history of fever (38.4° C) and generalized arthralgia. Her medical history revealed only minimal arteriosclerotic heart disease and mild arthritis for which she took ibuprofen as needed. On initial examination, she had increased intraocular pressure (52 mm Hg) and corneal edema. The anterior chamber was grossly clear as were the lens and vitreous cavity. A tentative diagnosis of glaucomatocyclitic crisis was made, and the patient was treated with cyclopentalate, topical corticosteroids, and acetazolamide. However, her pain was not relieved, and she was subsequently admitted to the hospital for further diagnostic examination and treatment. The first laboratory studies, including hemoglobin, leukocyte count with differential, SMA 12/60 profile, and electrolytes were all normal. On the second day of hospitalization, a darkly pigmented hypopyon developed, and a diagnostic anterior chamber paracentesis was performed. While awaiting culture results, the patient began receiving systemic intravenous cephalothin combined with subconjunctival betamethasone and triamcinilone acetonide. Approximately 72 hours after paracentesis, the laboratory reported the presence of *L. monocytogenes*, which was interpreted as a probable contaminant. However, during the next several days, the pigmented hypopyon recurred, and the patient was referred here for further examination.

Ocular examination revealed a visual acuity of R.E.: hand motion at six inches with good light projection; L.E.: 6/6-1 (20/20-1). Her left eye appeared to be normal. The right eye had a fixed, dilated pupil as a result of medication. The visual field was considered to be full to light perception. External examination of the right eye revealed a protective blepharoptosis and 2+ diffuse conjunctival injection. Slit-lamp biomicroscopy showed 3+ full thickness corneal edema. The anterior chamber had a large, inferior, darkly pigmented hypopyon that was mixed with fibrin. Pigment surrounded the edge of the pupil which appeared to originate from the posterior chamber (Fig. 1). There were some prominent temporal iris blood vessels, but no evidence of any iris mass. Fundus details could not be seen on dilated indirect ophthalmoscopy. However, no gross lesions were found. No mass lesions could be demonstrated by ultrasonography by means of the Bronson A- and B-scans or the water emersion Bronson B-scan.

After three days, the patient was admitted here with a presumptive diagnosis of a necrotic ciliary body melanoma. An anterior chamber paracentesis was performed for culture and histopathology. Histopathology showed macrophages laden with pigment without any evidence of tumor cells (Fig. 2). The cultures showed a significant growth of *L. monocytogenes* at 36 hours both in thioglycolate media and on sheep blood agar at 37° C. A gram-stained smear from a colony on the blood agar showed the typical appearance of *L. monocytogenes* (Fig. 3). A consultation was obtained from the infectious disease service, and the patient began receiving 20 million units/ day[1] of systemic intravenous penicillin for ten days, and 9.1 mg/ml of topical fortified

From the Bascom Palmer Eye Institute/Anne Bates Leach Eye Hospital, Department of Ophthalmology, University of Miami School of Medicine, Miami, Florida. This study was supported in part by Fight for Sight, Inc., Grant in Aid No. G-598; Fight for Sight Postdoctoral Research Fellowship No. 316; and the Florida Lions Bank. Dr. Abbott was a Heed Foundation Fellow (1977-1978).

Reprint requests to Richard K. Forster, M.D., P.O. Box 520875, Miami, FL 33152.

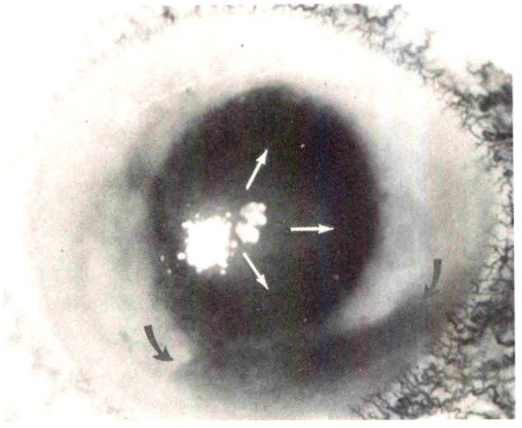


Fig. 1 (Abbott, Forster, and Rebell). Presence of an inferior, darkly pigmented hypopyon in the anterior chamber (black arrows), with pigment emanating from the posterior chamber at pupillary margin (white arrows).

gentamicin sulfate drops. Additionally, a repeat anterior chamber paracentesis was performed followed by an intracameral injection of 0.25 mg of cephaloridine. Within 18 hours, the culture from the anterior chamber grew *L. monocytogenes*. A medical examination including an echocardiogram, liver scan, routine x-ray films, and blood cultures was done to determine or rule out an occult infectious source. All these tests were negative. After five days of therapy, the patient underwent a third anterior chamber paracentesis, which subsequently proved to be culture-negative. At the time of the paracentesis, she received a second intraocular injection of 0.25 mg of cephaloridine.

The patient's vision gradually improved during the remainder of the hospital stay, and she was discharged to the care of her local ophthalmologist 14 days after admission with a visual acuity of 6/300 (4/200) in the right eye and an intraocular pressure of 40 mm Hg. Medications prescribed on discharge included fluorometholone, 0.25% scopolamine drops, and 125-mg tablets of acetazolamide.

The patient returned to us for a six-month follow-up visit. Ocular examination revealed a visual acuity of R.E.: 6/1200 (1/200). The cornea showed 2 to 3+ edema with prominent pigment clumping on the endothelial surface. Additionally, there was pigment deposition on the iris border, but the anterior chamber was deep and appeared clear. The intraocular pressure measured 46 mm Hg by Mackay-Marg tonometry, and a significant cataract was noted. The fundus examination was grossly normal. A bright flash electroretinogram was obtained and showed a normal A-wave and a slightly decreased B-wave. A trabeculectomy was performed with subsequent control of the intraocular pressure.

Discussion

Endogenous metastatic endophthalmitis may occur in systemic infections in which pathogenic organisms reach the eye via the blood stream.[3] Numerous published case reports have documented an underlying primary site of infection.[4–11] In many other cases, however, the pre-

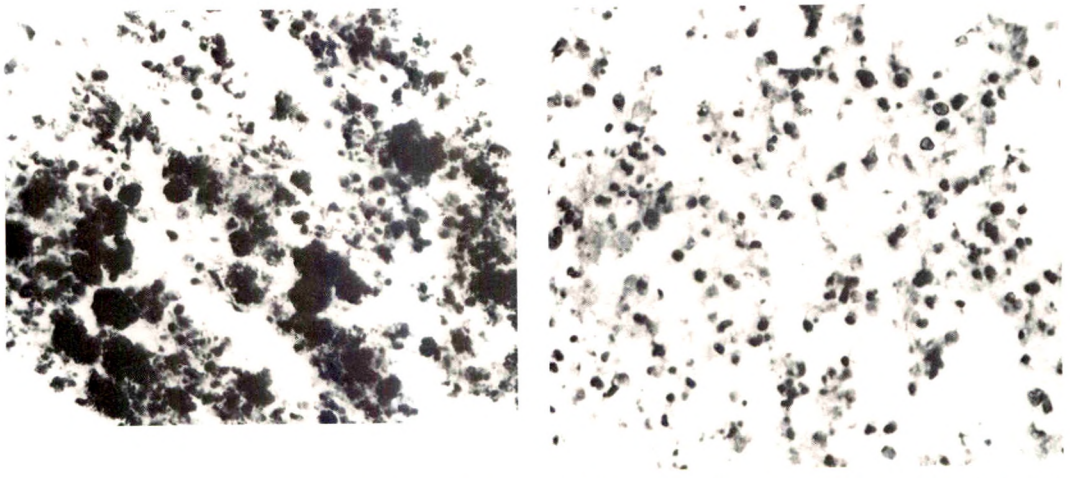


Fig. 2 (Abbott, Forster, and Rebell). Aqueous humor cytology. Left, Plump macrophages distended with ingester melanin comprise the black hypopyon observed clinically. Right, Bleached preparation permits examination of benign nuclear morphology of cells comprising inflammatory exudate (hematoxylin and eosin, ×700).

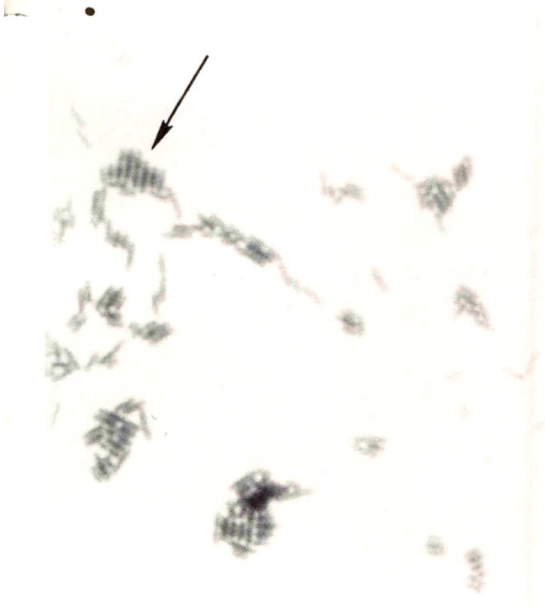


Fig. 3 (Abbott, Forster, and Rebell). A gram-stained smear of *Listeria monocytogens* showing the typical bacilli in palisade arrangement (arrow) (×420).

sumed underlying septic focus remained obscure. The event of clinical endophthalmitis as a complication of septicemia is, fortunately, rare.[3] We reviewed 108 consecutive cases of endophthalmitis referred here during a nine-year period and found 11% (12) of the total cases had an apparent metastatic origin with 40% (5) of these being infected. A history of illicit intravenous drug use was found in 40% of the metastatic cases. Most cases of endophthalmitis, however, were related to surgical procedures or to local trauma.

The occurrence of an endogenous endophthalmitis caused by the bacterium *L. monocytogenes* has been previously reported on only three occasions.[12–14] All of these cases were in elderly white men who initially had red, irritated eyes with decreased visual acuity and markedly increased intraocular pressures. In none of these previously reported cases was a pigmented hypopyon noted. In all cases the patients were first treated with topical corticosteroids and mydriatics for acute anterior uveitis without significant improvement. Once a diagnosis of metastatic endophthalmitis was suspected, the anterior chamber or vitreous cavities were cultured and the organism recovered. Each of the patients was then treated with conventional antibacterial therapy (topical, subconjunctival, and intravenous), but none recovered visual acuity better than 6/60 (20/200) (Table).

In our case, an elderly woman had similar symptoms of a red, irritated eye, with poor vision and increased intraocular pressure. As in the previously reported cases, the systemic examination for a possible extraocular nidus of infection was unproductive despite a two-day history of fever and arthralgias. On the second day of hospitalization, the patient developed a darkly pigmented hypopyon that appeared to be mixed with fibrin and adherent to both the corneal endothelium and iris surface. The appearance of this black hypopyon strongly suggested to many observers here that this possibly represented an occult, necrotic intraocular tumor. Albert and associates[2] reported two cases of intraocular melanoma with a black hypopyon in eyes with opaque media. One case had a primary choroidal melanoma, and the second case was metastatic to the uveae from a cutaneous melanoma. Histologic examination of the black hypopyon revealed pigment-laden macrophages and neoplastic melanoma cells. These pigment-containing cells tended to adhere to surfaces such as the corneal endothelium, iris, lens, and vitreous bands.

Our patient was taken to the operating room for a repeat diagnostic anterior

TABLE

SUMMARY OF FOUR CASES OF *LISTERIA MONOCYTOGENES* ENDOPHTHALMITIS

Case No.	Age, Sex (yrs)	Initial Visual Acuity	Final Visual Acuity	Initial Diagnosis	Initial IOP* (mm Hg)	Time between Onset of Disease and Treatment (days)
1 (Goodner and Okumoto)[12]	76,M	6/60 (20/200)	6/60 (20/200)	Anterior uveitis and corneal edema	43	14
2 (Bagnarello and associates)[13]	68,M	L.P.†	HM‡	Anterior uveitis and corneal edema	68	20
3 (Snead and associates)[14]	62,M	H.M.‡	6/120 (20/400)	Anterior uveitis and corneal edema	44	5
4 (Present Case)	68,F	H.M.‡	6/1200 (1/200)	Pigmented hypopyon and corneal edema	52	25

*IOP designates intraocular pressure.
†L.P. designates light perception.
‡H.M. designates hand motion.

chamber paracentesis to look for evidence of neoplastic cells and to repeat the bacterial culture. Careful examination of this material revealed no evidence of tumor cells (Fig. 2). However, the repeat culture was again positive for *L. monocytogenes.*

The patient was treated with both conventional and intraocular therapy to rapidly eradicate the intraocular infection. According to antibiotic sensitivities, the patient received intracameral injections of 0.25 mg of cephaloridine on two occasions combined with 9.1 mg/ml of hourly topical fortified gentamicin drops and 20,000,000 units of systemic intravenous penicillin in divided doses. Unfortunately, the additional use of intraocular antibiotics in combination with conventional therapy did not significantly alter the vision of our patient as compared to the vision of those in the previously reported cases.

L. monocytogenes is ubiquitous and has been reported with increasing frequency as a pathogen in healthy individuals without underlying disease.[1] Our case emphasizes many of the similarities that seem to be associated with *L. monocytogenes* endophthalmitis. All cases to date occurred in elderly patients in good physical health who had acute iridocyclitis with markedly increased intraocular pressure. Despite vigorous antibiotic therapy, no patient achieved a visual acuity of better than 6/60 (20/200). In three of the four cases, appropriate antibiotic therapy

was not started before 14 days following the onset of symptoms (Table). Earlier recognition of this infection and earlier initiation of antimicrobial therapy may achieve better visual results.

SUMMARY

A 68-year-old woman had a marked decrease in visual acuity, increased intraocular pressure, and acute iridocyclitis. She developed a pigmented hypopyon simulating an occult intraocular melanoma. Two anterior chamber paracenteses showed growth of *Listeria monocytogenes*. The patient received systemic intravenous penicillin, topical fortified gentamicin sulfate drops, and intraocular injections of cephaloridine. On discharge from the hospital after a two-week stay, visual acuity had improved and intraocular pressure had decreased.

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MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

THE TWENTIETH ANNUAL RESEARCH MEETING OF THE DEPARTMENT OF OPHTHALMOLOGY UNIVERSITY OF TORONTO

The 20th Annual Research Meeting of the Department of Ophthalmology, University of Toronto, Ontario, Canada,was held June 9, 1978, in the Medical Sciences Building of the University of Toronto. The meeting was inaugurated by Professor V. Kalnins of the Department of Anatomy, University of Toronto who spoke on the fiber systems of cells.

Abstracts of the scientific papers presented are as follows:

THE NATURE OF STORED SCLERA AND ITS FATE AFTER IMPLANTATION

M. Brown, P. M. H. Cherry, and P. K. Basu

In order to investigate whether scleral sutures could be banked, the effects of irradiation on the tensile strength of scleral strips (3 mm wide) made from human and rabbit eyes were tested. The tensile strength of the sutures following subcutaneous implantation was also studied.

With regard to the tensile strength, radiation reduced breaking elongation and elasticity, but did not significantly reduce work of rupture. Implantation produced a significant drop in tensile strength with respect to breaking load and work of rupture; and the decrease in breaking load was significantly greater for the irradiated sutures. There was no significant difference in any factor of tensile strength with respect to the locations in the globe from where the sutures were cut. Survival of the implant was related to host response and infection and was not related to radiation. Histologic examination showed the implants to be surrounded by thin connective tissue capsule and not invaded by host fibroblasts or vascular tissue.

NEW METHODS FOR TREATMENT OF FACIAL NERVE PARALYSIS

M. J. Howcroft, J. Hurwitz, and W. Gentles

Two methods for the prevention of ocular complications secondary to unilateral facial nerve paralysis were presented. The first consisted of a spectacle device with a sensing apparatus over the uninvolved eyelid to detect a normal eyelid closure. This blink was used to trigger a mechanical closure of the paretic eyelids via small levers resting on the upper and lower eyelids. Patients were therefore able to minimize corneal exposure changes and ectropion. Eyelid laxity was improved, resulting in a better cosmetic effect.

Investigation was also carried out in rabbits with surgically induced facial nerve paralysis. Electrodes implanted in the upper and lower eyelids were used to stimulate the orbicularis oculi directly via a miniature stimulator and battery source.

THE ASSESSMENT OF ENDOTHELIAL CELL COUNTS WITH THE SPECULAR MICROSCOPE

E. Mednick and C. Breslin

The specular microscope was used in rabbit models to evaluate the magnification and the area necessary to obtain reliable cell counts. Further studies compared central and peripheral cell counts.

The reliability of the specular microscope counts was then tested by comparing cell counts, using the specular microscope to estimate cell counts of stained histological endothelial specimens.

The 20-power objective was believed to be the most practical magnification to use in estimating endothelial cell counts. One field (area = 0.015 mm^2) was sufficient to give reliable counts in the normal rabbit endothelium when central and peripheral cell counts were compared ($P < .05$). A difference of approximately 10% was found between central and peripheral endothelial cell counts with more cells being central. A reasonable correlation ($P < .05$) between histologic specimen counts and specular photomicrography counts was found. This suggests that the specular microscope is a reliable indicator of endothelial cell densities.

The Value of Ultrasound In Intraocular Lens Power Calculation

E. M. T. Moniz and M. S. Kazdan

The value of ultrasonography in the calculation of intraocular lens power before implantation was studied in 21 eyes of patients who underwent primary implantation. The observed postoperative refraction was compared with the calculated for a standard 18.50-diopter lens. For the calculated lens power (with addition of +1.00 diopter) 48% were <1.50 diopters; 85% <3.00 diopters; 95% <4.50 diopters; and only 5% of the errors were >6.00 diopters. Refractive errors calculated for a standard 18.50 lens did not differ significantly from the above values; 62% were <1.50 diopters; 90% <3.00 diopters; and no errors were >6.00 diopters. It appeared that one can achieve similar results with either an 18.50-diopter standard lens or by calculating the power by ultrasound.

Electroretinograms In Zinc-Deficient Rats

M. Motolko, A. V. Rao, Y. Matuk, and J. Parker

The effects of dietary zinc deficiency on the electroretinograms of adult male rats and pups nursed by zinc-deficient mothers were examined. In one experiment, six 80-day-old rats were given a zinc-deficient diet. A second group of six rats served as pair-fed controls. At the end of a five-month period, the zinc-deficient group showed growth retardation, fluctuating patterns of food intake, and hair changes. These zinc-deficient adults showed significantly lower levels of zinc in feces and hair as well as histologic signs of testicular atrophy. Liver and retina zinc levels and electroretinograms remained comparable to controls. In another experiment, pups nursed for 21 days by a zinc-deficient mother were examined. These animals had significantly lower weights, depressed electroretinograms, and lower total body zinc levels than control groups.

The existence of stable and labile pools of zinc were postulated. Some tissues such as hair and testicles were more sensitive to zinc deficiency, whereas liver and retina were less easily depleted. The effects of zinc deficiency on electroretinograms might be caused by decreased vitamin A levels or decreased opsin synthesis reflecting the decreased protein synthesis of zinc deficiency.

Wound Healing of Trabeculectomies In Rabbits

A. Seetner and J. D. Morin

The wound healing of trabeculectomies in rabbit eyes was observed with photographs, fluorescein filtration, and histologic sections. Initially all except one animal developed blebs and had proven

filtration. However, vigorous fibroblastic proliferation (and collagen production) from the subconjunctiva, uvea, and sclera combined to close off the fistula by day 14. Groups of rabbit eyes treated with 8 mg of prednisolone injected subconjunctivally at the time of surgery showed slightly delayed wound healing, but by day 30 there was little difference between treated and untreated groups. Interestingly, the corticosteroid-treated eyes manifested complications ranging from endophthalmitis in one eye to tissue necrosis in three eyes.

Experimental Chloroquine Toxicity in Albino Rats

L. Tamaki and M. Ghosh

The purpose of the experiment was to study the pathologic changes in the cornea and retina of 40 rats receiving intramuscular injections of chloroquine hydrochloride twice weekly.

After nine weeks of injections most of the surviving rats were found to have a punctate epithelial keratopathy. Light microscopy of the corneas of affected rats revealed PAS-staining material at the junction between the basal and wing cell layers of the epithelium; electron microscopy revealed complete obliteration of the cell membranes of the basal cells caused by the deposition of hyaline granular material.

The retinas of rats with the keratopathy revealed intracellular bodies in several retinal layers. Electron micrographs of the retina of a rat injected twice weekly with 10 mg of chloroquine for 28 weeks, revealed massive aggregations of round or oval electrondense bodies in pigment epithelial cells. Membranous cytoplasmic bodies were found in ganglion cells and in Müller cell footplates. The inner nuclear layer was scattered with electrondense bodies as seen in the pigment epithelium. Similar findings were not observed in a rat killed at the same time, who had been receiving 8-mg injections twice weekly.

P. K. Basu

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NONVASCULAR PROLIFERATIVE EXTRARETINAL RETINOPATHIES

The pathologic features of extraretinal cellular proliferations have been recognized for many years.[1] Only recently, however, as retinal and vitreoretinal operations have been perfected, has their true significance been appreciated. Too often these lesions on the retinal surfaces become the limiting factor in otherwise successful retinal detachment operations.[2,3] While for many years these complex and severe proliferative lesions have frustrated retinologists in the clinic, recent laboratory studies in enucleated eyes have identified and characterized a variety of other similar lesions of simpler composition.[4–7] Thus, we now recognize a group of conditions covering a broad spectrum, from simple to complex, that can be classified as "nonvascular proliferative extraretinopathies." These conditions have the following in common: they arise from nonvascular tissue; they are proliferative in nature; and although they fundamentally affect the retina (causing wrinkling, folding, and detachment), they are extraretinal, occurring outside its anatomic limits, either on the inner (vitreous) surface or on the outer retinal pigment epithelium surface when the retina is detached.

On one end of this spectrum of seemingly diverse conditions is a benign spontaneously occurring lesion called "simple epiretinal membrane," in which accessory glial cells migrate from the superficial retina through surface breaks and form delicate cellular membranes on the retinal surface.[5] These membranes are common in enucleated eyes, although they are extremely subtle clinically and rarely cause significant visual problems.

At the other extreme of nonvascular proliferative extraretinopathy lesions is a complex condition usually complicating operations for retinal detachment, in which the detached retina becomes rigid, develops fixed folds, and along with the vitreous becomes sprinkled with pig-

ment-laden cells. The outcome in such cases is usually irreversible blindness. Initially this explosive process was attributed to alterations in the vitreous body and was labeled "massive vitreous retraction."[2] More recently several alternatives have been offered that pathogenically implicate either neuroectodermal or mesodermal derivatives as the fundamental cause. The most recent theory, and one of the few based on experimental pathology, strongly implicates the pigment epithelium.[8] Since retroretinal proliferation also accompanies the epiretinal membranes, the authors labeled the process "massive periretinal proliferation."

Between these extremes, clinical studies have recognized several apparently intermediate conditions with poorly characterized pathologic features but which appear to have the fundamental features of nonvascular proliferative extraretinopathy. These include "cellophane maculopathy,"[9] "macular pucker,"[3] "surface wrinkling retinopathy,"[4,6] "preretinal membrane,"[7] "preretinal macular fibrosis,"[10] "star folds," and recently "preretinal pigmented membranes."[11] How these lesions differ or interrelate is presently unknown. There is probably some overlap and even duplication, but this can be resolved only in the future by careful clinicopathologic correlative studies.

Of the lesions of intermediate complexity, surface wrinkling retinopathy is perhaps the better known at present.[4,6] We now recognize that surface wrinkling retinopathy occurs commonly as a spontaneous lesion in a significant portion of adults, reaching an incidence of over 20% of elderly patients.[6] At the present, this lesion appears to have many features in common with simple epiretinal membranes, but additionally is accompanied by wrinkling of the retinal surface and, sometimes by mild to moderate visual alterations.

With regard to the fundamental cause of nonvascular proliferative extraretinopathy, studies of enucleated eyes have confirmed the pathogenic importance of the retinal accessory glia in the simpler lesions,[5] and recently these cells have been shown to be present also in some of the more complex lesions.[12] The work of Machemer and colleagues,[8] however, indicates that proliferating retinal pigment epithelial cells dominate the picture in the more complex processes such as "massive periretinal proliferation." If the findings in the recent clinical report by Robertson and Buettner[11] of "pigmented preretinal membranes" are confirmed pathologically, the retinal pigment epithelium may also cause simple preretinal lesions in eyes with full-thickness retinal breaks and thus have as widespread a distribution in the nonvascular proliferative extraretinopathy spectrum as has been proven for the retinal accessory glial cell.

The extraretinopathies now being considered characteristically do not contain "true" fibrous tissue, that is, typical type 1 collagen derived from fibroblasts (or similar mesenchymal cells).[13] Such cells are found within the vitreous cavity only together with extraretinal or extrapapillary vessels in development anomalies or as part of an acquired process (for example, diabetic retinopathy[14,15]). Notwithstanding, proliferative vascular (mesodermal) and nonvascular (neuroectodermal) lesions may coexist, as has been shown clinically in diabetics.[14] Although little is known about the interrelationship of these classes of lesions, clinical experience suggests that several natural and iatrogenic factors can influence the progression as well as the severity of the fundamental process.[14] These conditions include inflammation[6]; hemorrhage (especially into the vitreous)[16,17]; trauma with mesodermal organization (where injury involves the uvea)[18]; and possibly therapeutic procedures such as photoco-

agulation, diathermy, and cryotherapy. Recent clinical studies in retinal detachment patients, however, had challenged some of these widely held beliefs.[19] Although nonvascular proliferative extraretinopathy degenerative processes may be modified by conditions as indicated above, it is important to recognize that pathologic[1,5,6] and experimental[8] evidence has shown that nonvascular proliferative extraretinopathy degenerative processes can develop fully in the absence of these aggravating conditions.

Significant advances in science often are stimulated by the recognition of sometimes subtle similarities between seemingly diverse conditions. We must now consider nonvascular proliferative extraretinopathies as a distinct and related group of conditions. We must hope that such a consideration will determine whether lesions in this broad spectrum have separate unrelated causes, or as I currently believe, the same cause with either varied expression or with a progressive interrelationship.

ROBERT Y. FOOS

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CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper, with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

Macular Lesions in Alport's Disease

Editor:

In the study, "Macular lesions in Alport's disease" (Am. J. Ophthalmol. 84:532, 1977), B. C. P. Polak and B. L.

Hogewind documented the presence of whitish-yellow perifoveal dot-like lesions in Alport's disease. We suspect that these lesions are similar to the findings described in a preliminary report by Purriel and associates.[1] In our presentation on fundus changes in the hereditary nephropathies at the American Academy of Ophthalmology and Otolaryngology meeting in 1973, we showed fundus photographs of similar lesions and described these in our subsequent published report.[2] In our patient, the perifoveal lesions were less prominent than the other fundus changes observed.

W. SCOTT PETERSON, M.D.
DANIEL M. ALBERT, M.D.
Boston, Massachusetts

Reply

Editor:

The lesions we described differ from the findings of Peterson and Albert in several ways. The fundus changes in their patients, similar to those reported earlier by Purriel and associates,[1] consist of desintegration of the retinal pigment epithelium, seen ophthalmoscopically throughout the fundus and mostly concentrated in the midperipheries. Fluorescein angiography of these lesions showed hyperfluorescent window effects, typical of a widespread disturbance of the retinal pigment epithelium. In contrast, the findings in our patients were confined to the most superficial retinal layers in the perifoveal areas and were not visible fluorographically.

BETTINE C. P. POLAK, M.D.
BAREND L. HOGEWIND, M.D.
Leyden, The Netherlands

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Optic Nerve Infarction

Editor:

We read with interest the report, "Optic nerve infarction," by P. R. Lichter and J. W. Henderson (Am. J. Ophthalmol. 85:302, 1978), which draws attention to an entity the authors called "optic disk infarction," characterized by acute visual field loss with optic disk atrophy and cupping in the presence of normal intraocular pressure and outflow facility. We too have seen individuals with apparent glaucomatous cupping and hemorrhages on the disk, together with field loss bisecting fixation in normotensive eyes with normal outflow facility, and would agree that the clinical features of these eyes would tend to separate them from typical cases of chronic simple glaucoma. However, we do not think Drs. Lichter and Henderson have made a case for acute infarction of the optic disk sufficiently clearly; nor, although they draw attention to it, have they defined the role and importance of hemorrhages on the optic disk.

The authors suggest that, in Case 2, optic atrophy occurred during the three-week interval between onset of visual symptoms and ophthalmic examination, and infer, in Case 1 at least, that this interval (unstated) was even shorter. We would have considered that this period of time was too short for the disk changes described to have occurred, and wonder whether the symptoms could reflect sudden discovery rather than occurrence of field loss, and that both field loss and signs could have been present for a longer period. Acute lesions of the optic nerve producing nerve fiber bundle type field defects, such as acute ischemic optic neuropathy are associated with disk swelling and signs of obstructed axoplasmic transport[1] and are followed by loss of neurons producing circular enlargement of the optic cup[2,3] rather than the vertically enlarged cup with focal thinning of the neuroretinal rim seen in chronic glauco-

ma.[4] There has been no suggestion that an acute ischemic optic neuropathy occurred in any of our patients with the signs noted by Drs. Lichter and Henderson.

A hemorrhage noted on the optic disk is important for drawing attention to decompensation in the vascular network at the optic disk. Drance and associates[5] showed that glaucoma patients with observed hemorrhages on the optic disk lose visual field more rapidly than glaucoma patients for whom such a hemorrhage was never seen.

Our own observation on patients with hemorrhages at the optic disk, who had been observed with disk photography for at least five years, revealed six with chronic simple and seven with low tension glaucoma. In these patients, we found the hemorrhages to be short-lived, disappearing in weeks rather than months, only to recur at the same and other sites on the optic disk. The hemorrhages were not always associated with glaucomatous cupping, nor were they always followed by visual field loss. In the eyes that developed definite glaucomatous cupping, the process occurred over months rather than weeks. When a hemorrhage resolved in an eye with pre-existing glaucomatous cupping, it seemed to originate from apparently healthy rim tissue adjacent to the region of rim thinning.

In conclusion, we wish to thank Drs. Lichter and Henderson for drawing attention to the occurrence of acute symptoms in patients with glaucomatous cupping and field loss in the absence of increased intraocular pressure, although we doubt whether, on the evidence cited, they can call the entity optic disk infarction.

R. A. HITCHINGS, M.D.
J. GLOSTER, M.D.
London, England

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BOOK REVIEWS

Pseudophakos. Edited by Norman S. Jaffe, Miles A. Galin, Henry Hirschman, and Henry Clayman. St. Louis, C. V. Mosby, 1978. Clothbound, 245 pages, table of contents, index, 257 black and white figures, $39.50

All ophthalmic surgeons are by now familiar with Ridley's serendipitous discovery that bits of Perspex could be tolerated by the eyes of the unfortunate pilots who received hits which shattered their Spitfire canopies. The rest is history and the implanting of an intraocular lens bids fair to becoming the most common eye operation done in the United States. This may or may not be appropriate and current studies should give some information on the validity of such widespread implantation. But in any case all those who feel that this is an appropriate operation should first read at least Chapter 2 of this book. Methylmethacrylate, the compound that is the base of almost all implants, is in reality a simple molecule that polymerizes easily; it is believed by all ophthalmologists to be an inert substance that lies quietly in the eye and causes no trouble. Unfortunately, it is not an inert substance and it does not necessarily lie quietly. Not only is it possible for the polymer to unzip, releasing a most destructive monomer, but the little bit of plastic that we do implant contains one or more of the following: fillers, plasticizers,

softeners, lubricants, heat stabilizers, antioxidants, stabilizers against dechlorination, flame retarders, blowing agents (whatever those are), cross-linking agents, and photodegradants. In all fairness this chapter is not all a horror story but a fascinating discussion of the chemistry of polymers. It is perhaps not immediately rewarding to the implant surgeon but this biochemist manque found it a delight.

Another chapter that is a must for all implanters is Chapter 4, on the history of the pseudophakos. The section on angle-fixated lenses is most illuminating. The authors describe the experience of one extremely competent European surgeon who implanted 493 anterior chamber lenses and eventually found it necessary to remove 250. If after perusing this chapter the reader still would like to continue his implantation then the rest of the book is available to give him guidelines for intraocular lens implantation; a large section on the surgical techniques is also included. There is a special section on the intraocular lens in the pediatric patient, written by David Hiles, and although the concept is frightening it perhaps makes more sense than random insertion of intraocular lenses in the adult. In the adult an alternative will provide good vision. In the infant there is practically no mechanism that will prevent the amblyopia which ensues after congenital cataract surgery or after traumatic cataract surgery for that matter. A limited number of carefully controlled implantations in one eye of these infants warrants doing with careful follow-up.

Chapter 12 on complications is again a must, not so much to teach one what to do in case of disaster but to warn the novice of the possible untoward events that can occur. Finally, Chapter 13 gives the results of pseudophakos surgery derived largely from the personal experiences of the authors. Each of these experts has a slightly different surgical approach and although the numbers are small it would appear that the end results are about the same.

If one is going to perform implant surgery one should: first, take a course; secondly, scrub with an expert as his assistant; and thirdly, read this book and take to heart all the caveats. One should particularly read the list of contraindications in Chapter 5. It may well be that studies now underway will show no increase in the number of complications in implanted eyes over those that have had routine cataract surgery; but one thing is certain, it is only in eyes with implanted lenses that the complication of a dislocated pseudophakos can occur.

DAVID SHOCH

Standard Pseudoisochromatic Plates. By Hiroshi Ichikawa. New York, New York, Igaku-Shoin, 1978. Hardcover, 48 pages, 19 color plates. $35

This new set of pseudoisochromatic plates is designed to screen for red-green color defects and to separate and classify protan and deutan color defectives. The plates are constructed from uniform sized dots that form digits (embedded in a background) designed to resemble those found on electronically generated numeric displays (for example, pocket calculators). There are four demonstration plates to familiarize the testee with the form of the test. The authors suggest that two of the demonstration plates may be useful in diagnosing tritan defects. The ten screening plates are designed so that one numeral on each plate is visible to normal observers and the other is visible to the color defective observers. The plates use reasonably highly saturated colors. An observer is considered normal if eight or more of the numerals for normals are read correctly. Finally, there are five classification plates in which color defective ob-

servers may be distinguished as either protan or deutan on the basis of which of two digits on each plate can be read (or which of the two is more distinct). Three of these plates have colored digits on colored backgrounds; the other two have colored digits on gray backgrounds.

The test is designed to be administered under natural daylight from a north window or under artificial light of similar spectral composition. The plates are placed 75 cm from the observer and a maximum viewing time of three seconds is permitted. A limited number of scoring sheets of clear design are provided.

The plates are attractively designed and easy to administer. Evaluation of the test must be postponed until independent verification of the screening and classification efficiencies of the plates are reported.

JOEL POKORNY
VIVIANNE SMITH-POKORNY

The Fine Art of Prescribing Glasses Without Making a Spectacle of Yourself. By Benjamin Milder and Melvin Rubin. Gainesville, Triad Scientific Publishers, 1978. Clothbound, 436 pages, table of contents, index, 25 black and white figures, 5 tables. $32

Behind the whimisical title are many sound clinical observations of refractive problems and how they are best solved.

The general format is the presentation of clinical cases to illustrate various problems every refractionist is likely to encounter. Some of the case presentations demonstrate the clinical astuteness of the authors, others are cited to point out common mistakes that even the most experienced refractionist is capable of making.

There are 18 chapters: Hyperopia, Accommodation, Cycloplegia, Myopia, Astigmatism, Multifocal Lenses, Muscle Imbalance, Anisometropia, Cataract, Aphakia, Contact Lenses, Absorptive Lenses, Medical Problems and Refractive Error, Occupational Lenses, the Partially Sighted Patient, Psychodynamics of Spectacle-Wearing, the Art of Dispensing, and the Dissatisfied Refraction Patient.

In the introduction, two principles are enunciated, which are immodestly called Milder's Laws: (1) "Never contribute to a visual deficit"; and (2) "Don't rock the boat." The subsequent 400 pages are devoted mainly to showing how to "rock the boat" successfully.

There is little to quarrel about in the chapters on hyperopia, myopia, and accommodation. The authors discuss accommodative spasm at some length. I believe such spasm is most frequently iatrogenic in origin. The authors emphasize the use of cycloplegics. Their statement that refractionists frequently do not use cycloplegics is surprising. Where I come from, ophthalmologists use cycloplegics routinely for refraction.

Together with Milder's aphorism No. 2 about rocking the boat, which translated means don't make any unnecessary changes in the patient's spectacles, I would emphasize the importance of comfort. Patients vary greatly, but I think most of my patients are extremely impatient with any discomfort resulting from a change in their correction. This is especially true of patients with anisometropia. Long ago, Lancaster talked about "the dubious advantages of binocular vision," a statement with which Milder and Rubin concur, yet they seem to go to some length to force binocularity on anisometropic patients.

The chapter on cataract is particularly good. It will appeal to all ophthalmologists who are conservative in advocating surgery. The authors stress the importance of reading vision even when distance vision drops as low as 6/18 (20/60) or 6/21 (20/70).

The chapter on aphakia is also well done. The friendly optician of whom the authors frequently speak recently came to my office carrying an array of optical blanks for aphakic spectacles. These ranged from the 3-drop and 4-drop lenses at $150.00 per pair to simple lenticular spherical without cylinders at $8.00 per pair. The authors point out that when aphakic individuals become accustomed to one form of lens, changing that form frequently causes difficulty.

In the section on contact lenses no mention is made of peripheral corneal vascularization, often seen in long-duration hard contact lens wearers, which is sometimes so severe that patients are required to give up their lenses.

This text will be particularly useful to inexperienced refractionists, and since it is never too late to learn, experienced refractionists will also gain from reading it. The style is airy and humorous and many of the subjects are treated with levity.

I cannot close without mentioning the poetry that introduces each chapter and closes the book. I am a refractionist, not a poet, and I think that the same must be said for the authors.

DANIEL SNYDACKER

SYMPOSIA

Recent Advances in Ultrasound Diagnosis. By Asim Kurzak. Amsterdam, Excerpta Medica, 1978. Hardcover, 331 pages, table of contents, index. $52.25

I. DONALD: **Scope and limitations of newer ultrasonic techniques**

G. KOSSOFF: **Automated ultrasonic scanning techniques**

S. LEVI, J. KEUWEZ, AND I. BREDAEL: **Tissue characterization in vivo: a semi-automatic method**

B. BREYER AND B. VOJNOVIC: **Noise measurement in ultrasonic pulse echo systems**

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J. E. DRUMM: **The effect of the maternal environment on the fetal crown-rump length**

J. F. PEDERSEN: **Normal tables of crown-rump length, biparietal diameter and abdomen circumference. A preliminary report**

V. LATIN AND A. KURJAK: **A comparison between four ultrasonic methods for prediction of gestational age**

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G. GENNSER: **Fetal breathing movements. Introductory remarks**

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J. PATRICK: Measurement of human fetal breathing movements with a real-time ultrasonic scanner

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A. KURJAK: Direct ultrasonic diagnosis of fetal malformations and abnormalities

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FRANK W. NEWELL, M.D.
Editor-in-Chief
AMERICAN JOURNAL OF OPHTHALMOLOGY

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

Acta Ophthalmologica

THE ULTRASTRUCTURE OF THE DEEP LAYER OF THE LENS CAPSULE IN FIBRILLOPATHIA EPITHELIOCAPSULARIS, SO-CALLED SENILE EXFOLIATION OR PSEUDOEXFOLIATION. Seland, J. H. (Univ. of Bergen School of Med., Bergen, Norway). Acta Ophthalmol. 56: 335, 1978.

The epithelial surface of the lens capsule and the capsular surface of the epithelium have been studied in six cataractous lenses from persons with fibrillopathia epitheliocapsularis or so-called senile exfoliation or pseudoexfoliation by scanning electron microscopy. Five of the lenses came from eyes with capsular glaucoma. Three senile cataractous lenses have been used as controls and two of the control lenses came from eyes with simple glaucoma. The investigation revealed round, discoid plaques closely adherent to the capsule. The plaque surfaces had numerous smooth tentacle-like projections and matching pits in the underlying epithelium. These plaques were only found in fibrillopathia epitheliocapsularis lenses and corresponded both in size and location to the structure known as the deep or amorphous layer of the lens capsule. The findings indicate that the epithelial cells are the source of origin. (10 figures, 1 table, 25 references)—Author's abstract

CORTICOSTEROID RESPONSE IN DOMINANT CONGENITAL GLAUCOMA. Jerndal, T., and Munkby, M. (Univ. of Göteborg, Sahlgren's Hospi, Göteborg, Sweden). Acta Ophthalmol. 56:373, 1978.

The parents of six children with goniodysgenesis and hereditary infantile congenital glaucoma were tested with corticosteroid eye drops. Their response on provocation demonstrated a clear trend: in five families one parent of each couple responded with a tensional rise of 9 mm Hg or more, whereas the other parent responded with a rise of 9 mm Hg or less. Of the six parents with the greater response, five had glaucoma in their ancestry and displayed a distinct goniodysgenesis. The findings support the previously presented view that hereditary infantile congenital glaucoma is caused by a dominant goniodysgenesis with varying expressivity. The high corticosteroid response in the families in this study appears to be correlated to this goniodysgenesis. The inherited corticosteroid response is obviously not a specific genetic trait confined to families with simple glaucoma. (13 figures, 1 table, 20 references)—Authors' abstract

HLA HISTOCOMPATIBILITY ANTIGENS IN OPEN-ANGLE GLAUCOMA. Damgaard-Jensen, L., and Kissmeyer-Nielsen, F. (Dept. Ophthalmol., Univ. of Aarhus, Aarhus, Denmark). Acta Ophthalmol. 56:384, 1978.

HLA-typing of 125 patients with open-angle glaucoma (glaucoma simplex) showed no statistically significant deviations from a control series of 1,197 blood donors. Some earlier, but mutually inconsistent, reports contradict this result. The conclusion can be drawn from this and earlier investigations that at the present time, tissue typing has not been proved to be a useful tool in elucidating the etiology and heredity of open-angle glaucoma. (1 table, 14 references)—David Shoch

Archives of Neurology

FORCED DOWNWARD OCULAR DEVIATION. Simon, R. P. (Dept. Neurol., San Francisco Gen. Hosp., San Francisco, Calif.). Arch. Neurol. 35:456, 1978.

A total of 32 consecutively encountered patients, comatose from sedative-hypnotic drug overdose, were studied by caloric (oculovestibular) testing with ice water. A variety of induced lateral eye movements was observed. The most striking findings was that the induced lateral eye movements were followed (in 24 of 32 cases) by delayed forced down-

ward deviation of one or both eyes. The phenomenon of forced downward ocular deviation during oculovestibular testing of comatose patients should suggest the diagnosis of sedative-hypnotic drug overdose. (1 figure, 14 references)—Author's abstract

Archives of Ophthalmology

PROGRESSIVE CHORIORETINOPATHY AFTER RECEIVING THIORIDAZINE. Meredith, T. A., Aaberg, T. M., and Willerson, W. D. (Medical College of Wisconsin, Milwaukee, Wis.). Arch. Ophthalmol. 96:1172, 1978.

A distinctive appearance of the ocular fundus as a late complication of high doses of orally administered thioridazine hydrochloride (Mellaril) is described. Discrete nummular areas of loss of retinal pigment epithelium extended from the posterior pole to the midperiphery. Fluorescein angiography demonstrated loss of choriocapillaris in these zones. Atrophy of the remaining retinal pigment epithelium was progressive, with advancement of the edges of the atrophic zones and breakdown of bridges of retinal pigment epithelium separating them. Atrophy occurred after discontinuation of the drug and advanced without further exposure to it. Dark adaptation, the electroretinogram, and the electro-oculogram were abnormal in the late stages. Central visual acuity remained relatively good. (6 figures, 2 tables, 24 references)—Authors' abstract

EFFECT OF LONG-TERM WEAR OF HARD CONTACT LENSES ON CORNEAL SENSITIVITY. Millodot, M. (Univ. of Wales Inst. of Science and Technol., Cardiff, United Kingdom). Arch. Ophthalmol. 96:1225, 1978.

The effect of years of wear of hard contact lenses on corneal sensitivity has been evaluated. By testing 91 subjects who had worn lenses for up to 22 years and a control group of 42 people, it was found that corneal sensitivity diminished exponentially. However, in five subjects who had abandoned use of their lenses, recovery occurred within four months, indicating that the process is reversible. The loss of corneal sensitivity with hard contact lens wear ought to be heeded, since the eye is thus at a greater risk of infection. (3 figures, 14 references)—Author's abstract

British Journal of Ophthalmology

THE IMPORTANCE OF MEASURING CONTRAST SENSITIVITY IN CASES OF VISUAL DISTURBANCE. Arden, G. B. (Dept. Visual Science, Inst. Ophthalmol., London). Br. J. Ophthalmol. 62:198, 1978.

Contrast sensitivity is tested with patterns of dark and light vertical bars in which the relative luminance varies from maximum to minimum according to a sine curve. Holding the average luminance of the entire pattern constant, the variables of such gratings are the number of cycles per degree of visual angle and the amplitude of the variations in relative luminance. Normal subjects attain greatest contrast sensitivity at about 3 cycles/degree. At higher or lower spatial frequencies contrast sensitivity declines in the form of an inverted U. Such contrast sensitivity curves of patients with visual disturbances may contribute substantially to the characterization of the particular disturbance. The production of gratings for clinical use is fraught with problems. After much experimentation with different photographic and printing processes the author has designed a book consisting of six test sheets or plates each of which presents gratings subtending, when viewed at a distance of 57 cm, one of the following spatial frequencies: 0.2, 0.4, 0.8, 1.6, 3.2 or 6.4 cycles/degree of visual angle. On each sheet contrast varies in the direction parallel to the grating bars (with the Y-dimension). The recommended technique of using the plates is to start by exposing to the examinee (with a card of about the same albedo as the pattern) only the portion with the lowest, subthreshold contrast which produces the sensation of uniform grey. The occluding card is then slowly moved to expose portions with successively higher and higher contrasts until the grating becomes visible. At that point the position of the card is read off on an arbitrary arithmetic scale parallel to the bars and serves as score of contrast sensitivity for the particular spatial frequency. To obtain such scores with the author's book does not require experienced examiners nor special per-

ceptive skill on the part of the examinee. Most subjects in a general population perceive a "contrast threshold" (the emergence of a grating out of homogeneous grey) quite readily and consistently. Some of the data reported during the last two years already point toward areas of potential clinical usefulness of tests for contrast sensitivity. (3 figures, 6 tables, 41 references)—Peter C. Kronfeld

EFFECTS OF PILOCARPINE ON THE MORPHOLOGY OF THE HUMAN OUTFLOW APPARATUS. Grierson, I., Lee, W. R., and Abraham, S. (Dept. Ophthalmol., Univ. of Glasgow, Glasgow, Scotland). Br. J. Ophthalmol. 62:302, 1978.

The authors' material consisted of 19 human eyes with small malignant melanomas of the choroid and clinically as well as histologically normal anterior segments. Eight of the eyes had been treated with 2 or 4% pilocarpine four times before the enucleation. From the calottes not required for diagnostic pathology, meridional blocks of limbal tissues were removed and prepared for light and electron microscopy. The histological studies focussed on the relative position of the scleral spur and on the giant vacuoles in the endothelium lining the inner wall of Schlemm's canal. Considerable variations from section to section from the same eye and from one eye to the other were encountered, but several features clearly distinguished the outflow apparatus of the pilocarpine-treated group from the control group. Measurements in microphotographs of the angle subtended by the axis of the scleral spur with a line passing through the anterior and posterior limits of the scleral furrow revealed a highly significant difference ($P<.001$) between the pilocarpine-treated and the control eyes. This is interpreted as the result of increased pull on the scleral spur by the contraction of the ciliary muscle under the action of pilocarpine, making the spur move inwards and backwards. Consequently, the outer meshwork tissues are stretched and its layers more separated. Quantitative light microscopy also revealed more than twice as many giant vacuoles in the inner wall of Schlemm's canal of the pilocarpine-treated eyes as in the control eyes. Electron microscopy added the qualitative impression that both vacuolar and nonvacuolar transcellular channels were more frequent in the pilocarpine-treated eyes. Another effect of pilocarpine may be a washout of the extracellular, intertrabecular material which has been demonstrated in greater quantities in older eyes and is considered a major contributor to outflow resistance. (14 figures, 2 tables, 29 references)—Peter C. Kronfeld

ANGLE-CLOSURE GLAUCOMA SECONDARY TO POSTERIOR SCLERITIS. Quinlan, M. P., and Hitchings, R. A. (Dept. Clin. Ophthalmol., Inst. Ophthalmol., London). Br. J. Ophthalmol. 62:330, 1978.

The report deals with one episode, apparently the first, of unilateral posterior scleritis with secondary angle-closure glaucoma in three middle-aged male patients. The diagnosis of posterior scleritis was suggested by sudden onset, tenderness of the globe or actual deep ocular pain, fringes of anterior scleritis and gross, localized choroidal detachment. There were no or just minimal signs of an inflammatory process in the contents of the anterior chamber, but its axial depth was measurably less than that of the unaffected fellow eye. The chamber angle appeared closed and the pressures were moderately elevated. On treatment with topical cyclopentolate and epinephrine and oral oxyphenbutazone and acetazolamide, the chamber deepened, the angle opened and the pressure dropped to normal within a few days; the choroidal detachment resolved more slowly, requiring oral corticosteroids in one case. (10 figures, 16 references)—Peter C. Kronfeld

PIT-LIKE CHANGES OF THE OPTIC NERVE HEAD IN OPEN-ANGLE GLAUCOMA. Radius, R. L., Maumenee, A. E., and Green, W. R. (Wilmer Ophthalmol. Inst., Johns Hopkins Univ. School of Med., Baltimore, Md.). Br. J. Ophthalmol. 62:389, 1978.

The development of pit-like defects in the tissues of the nerve head near its inferior pole associated with corresponding progressive field defects was observed in one eye of six patients who had been followed and treated for open-angle glaucoma for a number of years. In three of the cases the ophthalmoscopic relationship between the pits and the typically glaucomatous changes of the disk is shown in photographs. Whether the pits are a result of elevated intraocular pressure acting on a weak spot in the lamina cribrosa or represent secondary changes following ischemic necrosis of nerve tissue, can not be determined from the available material. Clinically,

it is important to realize that pits in the disk surface can be a manifestation of glaucomatous optic nerve damage and that such patients should be carefully watched for the development or progression of field defects, particularly if the pressure is elevated. (4 figures, 10 references)—Peter C. Kronfeld

Canadian Journal of Ophthalmology

THE PREDICTIVE VALUE OF LEUKOCYTE MIGRATION INHIBITION TEST IN HUMAN KERATOPLASTY. Cherry, P. M. H., Basu, P. K., and Thompson, G. A. (Univ. of Toronto, Toronto, Ontario). Can. J. Ophthalmol. 13:194, 1978.

The authors compared the result of penetrating keratoplasty in 18 patients whose preoperative or immediate postoperative leukocyte migration inhibition tests were positive (>20% inhibition) with those in 15 patients whose leukocyte migration inhibition tests were negative. A negative leukocyte inhibition test indicated a greater chance of avoiding graft rejection ($P<.005$), and of ending up with a clear graft ($P<.05$). (4 tables, 21 references)—Authors' abstract

Investigative Ophthalmology and Visual Science

RHODOPSIN AND VISUAL THRESHOLD IN RETINITIS PIGMENTOSA. Ripps, H., Brin, K. P., and Weale, R. A. (New York Univ. School of Med., New York, N.Y.). Invest. Ophthalmol. Visual Sci. 17:735, 1978.

Rhodopsin kinetics and visual threshold were determined in three subjects with a dominant form of retinitis pigmentosa. The retinal areas studied showed varying loss of sensitivity, which correlated well with the reduction in the measured density of rhodopsin in the test region. Rhodopsin photosensitivity was normal, and there was no evidence that either rhodopsin or the cone pigments regenerated more rapidly than normal. The findings in these cases of retinitis pigmentosa, when compared with the threshold changes indiced by vitamin A deficiency or photic bleaching, suggest that the disease produces an imbalance between disk removal and new disk formation, which results in progressive shortening of the photoreceptor outer segments and, eventually, in their complete disappearance. (7 figures, 2 tables, 44 references)—Authors' abstract

Journal of the American Medical Association

EXOPHTHALMOS IN SEMINOMA. Taylor, J. B., Solomon, D. H., Levine, R. E., and Ehrlich, R. M. (Dept. Surg., Univ. of California School of Med., Los Angeles, Calif.). J.A.M.A. 240:860, 1978.

A 57-year-old man had a two week history of progressive protrusion of the eyes, decreasing visual acuity, and limitation of eye movements. All thyroid studies were normal as was a bone marrow smear. Because of the severity of visual impairment, prednisone therapy was started in large doses with swift improvement. Vision returned to 6/6 (20/20). However, when the corticosteroids were stopped, the proptosis and eye restriction returned. Corticosteroids were again started with clearing of the eye findings. At this time a three by three centimeter mass was found in the left testis and an orchiectomy revealed a seminoma. The corticosteroid therapy was stopped and there was no recurrence of the ophthalmopathy over a four-year period. The cause of exophthalmos in seminoma is unknown but in two of the three cases reported in the literature there have been elevated human chorionic gonadotrophin levels. Patients who have euthyroid Graves' ophthalmopathy in the absence of thyroid disease should be screened for the presence of seminoma and perhaps for other occult neoplasms with known endocrine potential. (5 references)—David Shoch

Klinische Monatsblätter für Augenheilkunde

FLUORESCEIN ANGIOGRAPHIC STUDY ON THE RETINAL VESSELS OF YOUNG CIGARETTE SMOKERS. (German) Gartner, J., and Noah-Duesberg, C. (Univ. Eye Clinic, Univ. of Mainz, Mainz, West Germany). Klin. Mb. Augenheilkd. 172:694, 1978.

A randomized blind study on 28 smokers and 30 non-smokers aged between 17 and 39 years, who were entirely healthy according to the results of physical and ophthalmoscopic examination, was undertaken with the aid of fluorescein angiography. Only smokers with a consumption of at least 15 cigarettes daily and a history of smoking for at least five years were taken into account for the study. The angiograms were read as fluorescein angiographic negatives under a stereo-microscope. Caliber irregularities of the retinal arteries, veins, arterioles and venules were found in 18 of the smokers and two of the non-smokers. The incidence of vascular irregularity in smokers is highly significant at the one percent level. (3 figures, 13 references)—Authors' abstract

Ophthalmologica

HISTOPATHOLOGICAL CHANGES IN SIDEROSIS BULBI. Appel, I., and Barishak, Y. R. (Asaf Harofe Hosp., Tserifin, Israel). Ophthalmologica 176:205, 1978.

The histopathology of indirect siderosis bulbi induced by iron intraocular foreign bodies which penetrated into the posterior segment of the eye, is reported. Iron ions disperse into the vitreous first and into the aqueous humor later and then they enter into all the tissues which surround the vitreous and the aqueous. Iron ions penetrate into the suprachoroidal space through the angle. (6 figures, 10 references)—Authors' abstract

IMPORTANCE OF THE VIABILITY OF THE ENDOTHELIUM ON THE CORNEAL GRAFT. (French) François, J., Victoria-Troncoso, V., Verbraeken, H., and Cansu, K. (Ghent, Belgium). Ophthalmologica 176:245, 1978.

Generally speaking the success of corneal grafting depends almost entirely on the viability of the donor endothelium. The authors were able to reduce their failures to a very low level by carefully examining the endothelium of the donor material. The gross donor eye is first examined by a biomicroscope and if there is guttata or a secondary endothelial dystrophy or too many folds in Descemet's, then the eye is rejected. If there are no obvious biomicroscopic defects, then the cornea is dissected off and placed in an aqueous solution of Trypan blue and examined under the microscope. If more than 30% of the endothelial cells take the dye, then the cornea is eliminated. If the cornea passes this test, it is then placed in a solution of toluidine blue and ten fields are then examined. Five of these fields are central and five are peripheral. If more than five fields take up the dye, then the cornea is also eliminated. In keratoconus, 50% endothelial viability suffices but in a patient with a bad corneal endothelium, it is necessary that 80 to 100% of the donor endothelium be viable. It should be pointed out that these various manipulations are done on one eye of a pair that has been enucleated and it is the unstained cornea that is used for the transplantation. Further, it should be pointed out that two days before the operation, immunosuppressive treatment is started, consisting of 50 mg of Imuran three times a day and this is generally continued for two months. With this routine the authors improved their success rate enormously. (6 figures, 1 table, 2 references)—David Shoch

Stroke

RELATIONSHIP BETWEEN OPHTHALMIC ARTERY BLOOD FLOW AND RECANALIZATION OF OCCLUDED CAROTID ARTERY. ULTRASONIC DOPPLER STUDY. Kaneda, H., Irino, T., Arita, N., Minami, T., Taneda, M., and Shiraishi, J. (Dept. Neuropsychiatry, Osaka Univ. Med. School, Osaka, Japan). Stroke 9:360, 1978.

The authors followed five patients all of whom showed angiographic evidence of occlusion of the internal carotid artery. At the time of the occlusion, Doppler studies were also done of the ophthalmic artery on the same side and in four of the five cases there was reversed flow of the ophthalmic artery and in one case no flow. Three to six weeks after the occlusion the angiography and the Doppler studies were repeated in two patients in whom the internal carotid had recanalized, there was a physiologically normal flow in the ophthalmic artery as measured by the Doppler study. In the three patients where there was nonrecanalization of the internal carotid, the reverse flow in the ophthalmic artery was maintained in two and there was physiologically abnormal flow in the third. It would seem that Doppler studies of blood flow in the ophthalmic artery might be a useful noninvasive way to follow the progress of internal carotid artery occlusions. This would avoid the necessity of repeated invasive angiographic studies. (4 figures, 2 tables, 8 references)—David Shoch

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.

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For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least three months before the date of occurrence.

TENTH ANNUAL JULES STEIN LECTURE

The Tenth Annual Jules Stein Lecture and Postgraduate Seminar will be presented at the Century Plaza Hotel, Los Angeles, California, April 19 and 20, 1979. The seminar topic is "Highlights of Neuro-Ophthalmology". The Jules Stein Lecture will be delivered by Thomas P. Kearns. The program chairmen are Robert S. Hepler and Robert D. Yee. For further information, write to Jules Stein Eye Institute, UCLA School of Medicine; Attention: Mrs. Lu Hendricks; Los Angeles, CA 90024.

XIV MEXICAN CONGRESS OF OPHTHALMOLOGY

The XIV Mexican Congress of Ophthalmology will be held April 22-27, 1979, in Veracruz, Veracruz, Mexico. For further information, write Leonard M. Rifkin, M.D., 176 W. College St., Covina, CA 91723; telephone (213) 331-4891.

AMERICAN ASSOCIATION FOR PEDIATRIC OPHTHALMOLOGY AND STRABISMUS: FIFTH ANNUAL MEETING

The American Association for Pediatric Ophthalmology and Strabismus will hold their fifth annual symposium at the Four Seasons Hotel, Toronto, Canada June 3-6, 1979. For further information and complete program, write J. S. Crawford, M.D., 555 University Ave., Toronto, Canada M5G 1X8.

CONFERENCE ON SUB-RETINAL SPACE

The Conference on Sub-Retinal Space will take place in Kubbutz Kiryat Anavim, Jerusalem, Oct. 14-19, 1979. The meeting will concentrate on the following: anatomy, physiology, biochemistry, experimental pathology, and clinical aspects. For further information, write Hanan Zauberman, M.D., Hadassah University Hospital, Eye Department, Jerusalem, Israel.

MIAMI OPHTHALMOLOGICAL SOCIETY: FIRST ANNUAL WINTER SEMINAR

The First Annual Winter Seminar of the Miami Ophthalmological Society, will be held at Vail, Colorado, Jan. 27-Feb. 3, 1979. For further information, write David J. Singer, M.D., Program Chairman and Secretary, Miami Ophthalmological Society, 1160 Kane Concourse, Miami Beach, FL 33154.

NASSAU SURGICAL SOCIETY: INTRAOCULAR LENSES SYMPOSIUM

The Ophthalmology Section of the Nassau Surgical Society will hold a symposium on intraocular lenses, management of problems and complications, Dec. 13, 1978, between 1 and 5 PM at the Nassau County Medical Center, Hempstead Turnpike, East Meadow, New York. For further information, write J. S. Nauheim, M.D., 2025 Merrick Ave., Merrick, NY 11566.

WILMER INSTITUTE: CURRENT CONCEPTS IN OPHTHALMOLOGY COURSE

The Wilmer Institute of the Johns Hopkins Hospital will present a course, "Current Concepts in Ophthalmology," at the Cerromar Beach Hotel, Dorado Beach, Puerto Rico, Feb. 19-23, 1979. The program will highlight the medical and surgical management of diseases of the cornea, lens, vitreous, and retina. The registration fee of $350 includes a banquet. Registration is limited to 100 participants. For further information, write to Walter J. Stark, M.D., Wilmer Institute, Johns Hopkins Hospital, 601 N. Broadway, Baltimore, MD 21205.

ECTOPIA LENTIS CAUSED BY HOMOCYSTINURIA: NIH REQUESTS CONTACT WITH FAMILIES

The cooperation of physicians is requested on a project to determine whether heterozygotes for homocystinuria, cystathionine synthase dificiency type, are at increased risk for some of the abnormalities prominent in homozygotes for this condition. —his project is currently being carried out by Harvey Mudd, National Institute of Mental Health, Bethesda, Maryland, and Harvey Levy, Massachusetts General Hospital, Boston, Massachusetts. They are soliciting the cooperation of any physician who is in touch with families with homocystinuric patients and who is willing to send a questionnaire to such families. The questionnaire is brief (one page) and concerns the health status of the parents and grandparents of affected patients. Interested physicians are asked to write Dr. Mudd (Building 32A, Room 101, NIMH, Bethesda, MD 20014) or to telephone him (301-496-3528) if there are questions. He will provide the questionnaire, as well as a suggested covering letter explaining the project to the family, and a consent form.

Patients with the cystathionine synthase deficiency type of homocystinuria often come to medical attention because of dislocation of the optic lenses, or complications secondary to such dislocation. Physicians who know of patients with ectopia lentis of uncertain cause are invited to submit urine samples from such patients. Amino acid analysis for homocystine is offered, at cost, by Dr. Harvey Levy, Amino Acid Laboratory, Massachusetts General Hospital, Boston, MA 02114 (telephone 617-726-3885) as a means of making the diagnosis. A small random voided specimen is satisfactory. Dr. Levy will send directions and a shipping container for the specimen.

Training Aids on Xerophthalmia

Eight prototype training aids for use in the prevention and treatment of xerophthalmia and keratomalacia are available from Helen Keller International, New York. The materials are aimed at health and nutrition personnel at all levels in developing countries.

The aids, prepared in cooperation with the Nutrition Foundation and with support from the Agency for International Development, are being used by ministries of health, hospitals, universities and medical schools, and public health centers to teach the best methods for eradicating child blindness brought on by malnutrition and lack of vitamin A.

The information ranges from latest scientific findings on the clinical diagnosis and treatment of nutritional blindness to simpler guides on the etiology, prevention, and treatment of the disease, and flip charts for use in teaching mothers the hazards of malnutrition and lack of vitamin A in a child's diet. Filmstrips, slide sets, plates, and illustrations are included.

The flyer, "Conquering Xerophthalmia," with descriptions of the aids and an order blank, may be obtained without charge by writing to Blindness Prevention Department, Helen Keller International, 22 W. 17 St., New York, NY 10011.

Research to Prevent Blindness: 1978 Trustees Award to Robert Machemer

Research to Prevent Blindness, Inc., presented its Trustees Award for Outstanding Ophthalmic Achievement to Robert Machemer Oct. 22, 1978, at the meeting of the American Academy of Ophthalmology in Kansas City, Missouri. Dr. Machemer was honored as "a physician and scientist whose creative genius has restored the gift of sight to many who would otherwise be hopelessly blind . . . by the introduction of pars plana vitrectomy . . . a revolutionary achievement which overcomes what once seemed an insurmountable obstacle to vitreous surgery, the extreme danger of attempting to remove opaque vitreous from the inner cavity of the eye without destroying its essential functions or the integrity of the globe."



Robert Machemer, M.D., recipient of the 1978 Research to Prevent Blindness Trustees Award.

The Research to Prevent Blindness Trustees Award consists of a citation and a $25,000 honorarium financed from the personal contributions of the trustees. The award was established in 1966 to recognize those who have made extraordinary contributions toward the preservation of sight.

Formerly at the Bascom Palmer Eye Institute of the University of Miami School of Medicine, Dr. Machemer became professor and chairman of the Department of Ophthalmology at Duke University Eye Center, Durham, North Carolina, in August 1978.

VISUAL FIELD CHARTS

Central and peripheral field charts are available without charge to authors who require them to illustrate their papers. Write to Editorial Correspondent, American Journal of Ophthalmology, 233 East Ontario Street, Suite 1401, Chicago, Illinois 60611.

INSTRUCTIONS TO AUTHORS

For the preparation of manuscripts for American Journal of Ophthalmology

THE AMERICAN JOURNAL OF OPHTHALMOLOGY publishes original and timely contributions dealing with clinical and basic ophthalmology. Each article submitted is evaluated by two or more referees who recommend that the paper be (1) accepted unchanged, (2) returned for revision and subsequent editorial consideration, or (3) rejected. Acceptance is conditioned by such factors as the originality, significance, and soundness of the contribution; the suitability of the subject matter for subscribers of THE JOURNAL; and, the care with which the manuscript has been prepared.

Papers are accepted on the condition that they have not been published or accepted for publication in any other journal, whether printed in English or any other language. On occasion, a paper read before a society and published in the society's transactions will be considered if the society publication does not reach as wide an audience as the contribution merits. When submitting such a paper, the author must indicate the time and place of the meeting and the name of the society publication. It is not possible to coordinate the date of publication of such papers in THE JOURNAL with that in the society publication.

Authors will be advised promptly of receipt of their papers. Thereafter they will be advised within 30 days of acceptance, rejection, or need for revision. Manuscripts that require extensive editorial correction or retyping will be returned for that purpose.

MECHANICAL PREPARATION OF MANUSCRIPT The manuscript should be prepared in the style used by THE JOURNAL. A heavy grade of white bond paper measuring 8½ by 11 inches should be used. Margins should be at least 1½ inches on all sides. Paragraphs should be indented at least one-half inch. Two copies must be submitted; carbon copies and machine-duplicate copies are acceptable only as second copies.

Instructions to Authors—CONT.

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The manuscript should be arranged in the following order:

1. Title page (with footnotes)
2. Text and summary
3. Acknowledgments
4. References
5. Tables
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Each major section should begin on a separate sheet.

TITLE PAGE The title page should be numbered page 1 and contain the running (abbreviated) heading, the title, each author's name and highest degree, and the city and state where the work was carried out. The institution and the organization(s) sponsoring the study should be credited in a footnote. A second footnote should give the name and mailing address of the author to whom correspondence should be directed. Each page after the title page should show the page number, senior author's name, and running title in the upper righthand corner.

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Summary—Each paper must have a summary that describes the content of the paper in no more than 150 words. The author should state precisely what was accomplished, and avoid generalities.

Acknowledgments—Sponsoring organizations and grants should be acknowledged in the first footnote on the title page. Other acknowledgments follow the summary.

REFERENCES The author is responsible for complete and accurate references, including the proper capitalization and accent marks used in foreign-language publications. References must be numbered consecutively, according to their appearance in the text. Extensive reviews of the literature are not desirable. Personal communications should be kept to a minimum. Reference to studies that have been accepted for publication, but not yet published, should indicate where they will be published. Reference to studies still in progress should be described as such in the text without a reference number. Primary, not secondary, sources should be cited; references derived from encyclopedic reviews or textbooks are seldom acceptable. References should be cited in the text as follows: Allen and Smith[1] and Jones[2] described . . .

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1. Terry, T. L.: Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens. Am. J. Ophthalmol. 25:203, 1942.

2. Reese, A. B.: Tumors of the Eye, 2nd ed. New York, Hoeber, 1964, p. 91.

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Fig. 1 (Jones, Smith, and Brown). Histologic section of the eye (hematoxylin and eosin, ×70).

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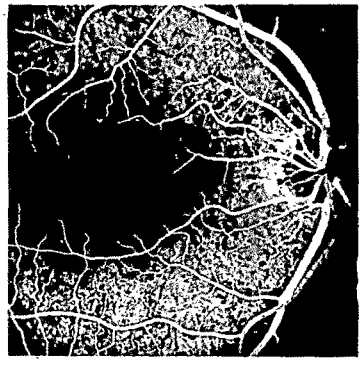
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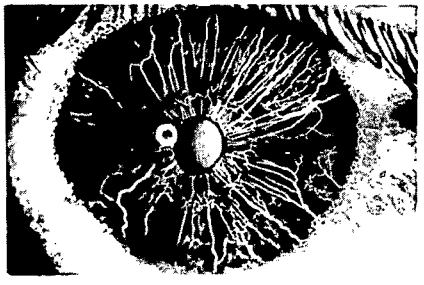
Council of Biology Editors, Committee on Form and Style: CBE Style Manual, 3rd ed. Washington, D.C., American Institute of Biological Sciences, 1972.

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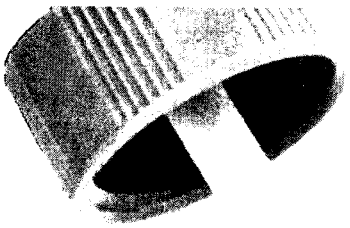
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PHOSPHOLINE IODIDE is a long-acting cholinesterase inhibitor for topical use.
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Contraindications: 1. Active uveal inflammation.

2. Most cases of angle-closure glaucoma, due to the possibility of increasing angle block.

3. Hypersensitivity to the active or inactive ingredients.
Warnings: 1. *Use in Pregnancy:* Safe use of anticholinesterase medications during pregnancy has not been established, nor has the absence of adverse effects on the fetus or on the respiration of the neonate.

2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patients receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.

3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same time undergoing treatment with systemic anticholinesterase medications for myasthenia gravis, because of possible adverse additive effects.
Precautions: 1. Gonioscopy is recommended prior to initiation of therapy.

2. Where there is a quiescent uveitis or a history of this condition, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.

3. While systemic effects are infrequent, proper use of the drug requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into the nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.

4. Temporary discontinuance of medication is necessary if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregularities occur.

5. Patients receiving PHOSPHOLINE IODIDE who are exposed to carbamate or organophosphate type insecticides and pesticides (professional gardeners, farmers, workers in plants manufacturing or formulating such products, etc.) should be warned of the additive systemic effects possible from absorption of the pesticide through the respiratory tract or skin. During

6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects.

7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.

8. PHOSPHOLINE IODIDE (echothiophate iodide) should be used with great caution, if at all, where there is a prior history of retinal detachment.
Adverse Reactions: 1. Although the relationship, if any, of retinal detachment to the administration of PHOSPHOLINE IODIDE has not been established, retinal detachment has been reported in a few cases during the use of PHOSPHOLINE IODIDE in aphakic patients without a previous history of this disorder.

2. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.

3. Activation of latent iritis or uveitis may occur.

4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.

5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.

6. Lens opacities occurring in patients under treatment for glaucoma with PHOSPHOLINE IODIDE have been reported and similar changes have been produced experimentally in normal monkeys. Routine examinations should accompany clinical use of the drug.

7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.
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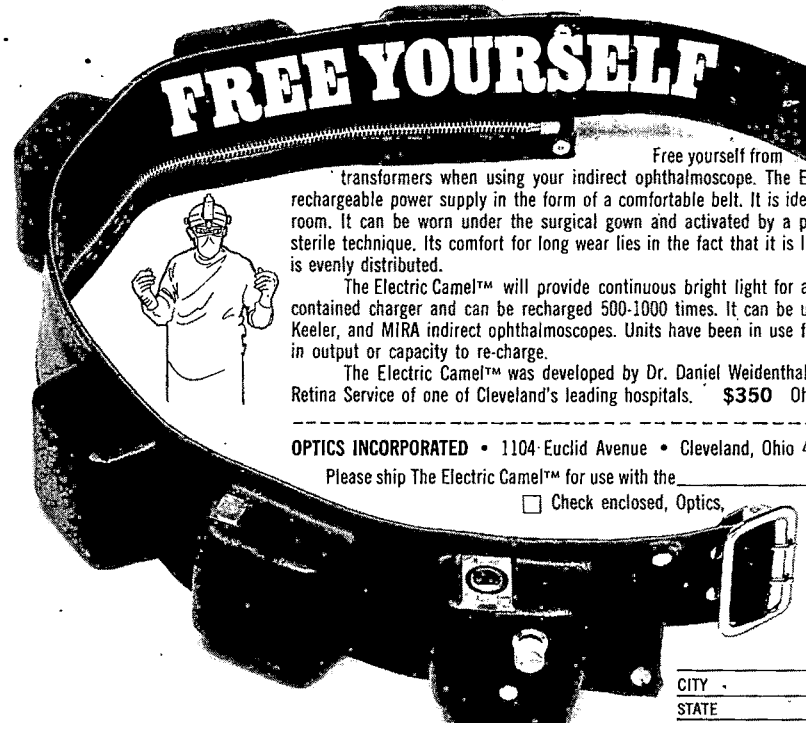
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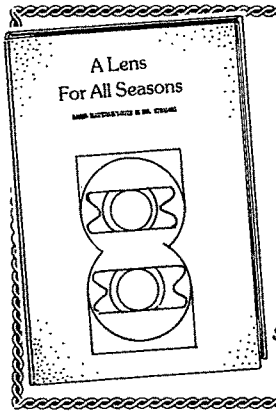
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STRABISMUS (4 hours)	Robert D. Reinecke, M.D.,Professor and Chairman, Department of Ophthalmology, Albany Medical College of Union University
CORNEA AND EXTERNAL DISEASES (4 hours)	Juan Arentsen, M.D., Assistant Professor, Jefferson University; Associate Director, Cornea Service, Wills Eye Hospital
PHARMACOLOGY AND THERAPEUTICS (4 hours)	Joel S. Mindel, M.D., Assistant Professor, Department of Ophthalmology, Mt. Sinai School of Medicine
GLAUCOMA AND METABOLIC DISEASES (4 hours)	Stephen M. Podos, M.D., Professor and Chairman, Department of Ophthalmology, Mt. Sinai School of Medicine
EMBRYOLOGY & ANATOMY (4 hours)	David M. Worthen, M.D., F.A.C.S., Professor and Head, Division of Ophthalmology, University of California San Diego
MEDICAL OPHTHALMOLOGY (4 hours)	Paul Henkind, M.D., Ph.D., Professor and Chairman, Department of Ophthalmology, Montefiore Hospital and Medical Center
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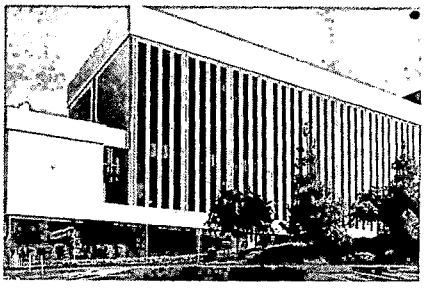
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Friday: Radiological Techniques in Orbital Diagnosis, Computerized Tonography, Ultrasound & Doppler in Orbital Diagnosis, Laboratory Diagnosis of Thyroid Disease, Drugs in Ocular Diagnosis, Background, Basics & Perspectives in Fluorescein Angiography, Retinal Vascular Disease, Diabetes, Intraocular Tumors, Iris Angiography, Macular Diseases,

Saturday: Melanotic Epibulbar Lesions & Syndromes, Cornea and Conjunctival Epithelial Tumors, Cytology in Ocular Diagnosis, Iris Tumors, Lid Lesions, Intraocular Melanomas, Oncology and Ocular Melanomas, Lymphoid Tumors, Electron Microscopy, Participating Workshops in Ultrasound, Pathology, Microbiology, Electrophysiology and Photography.

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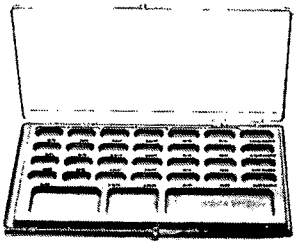
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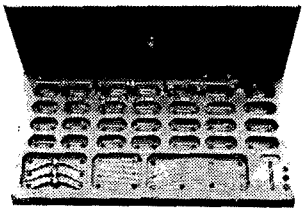
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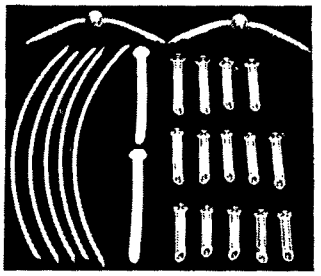
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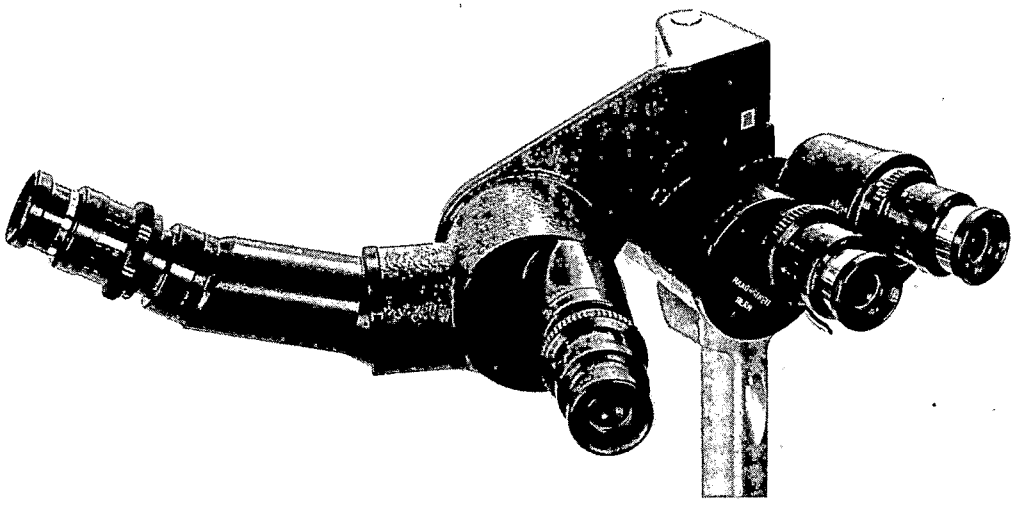
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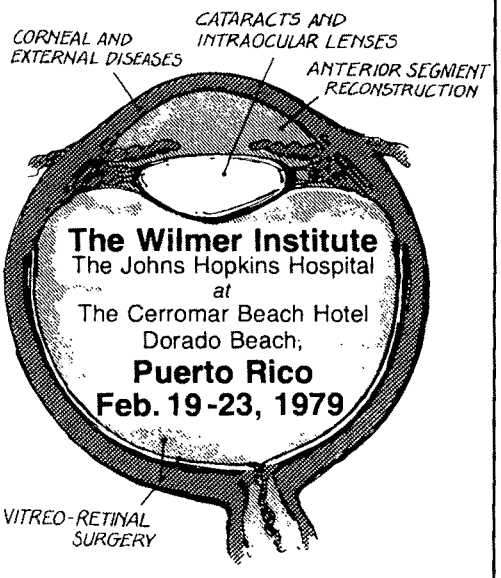
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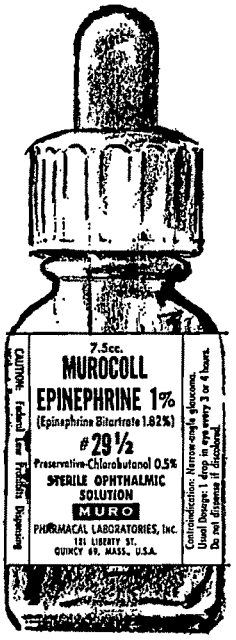
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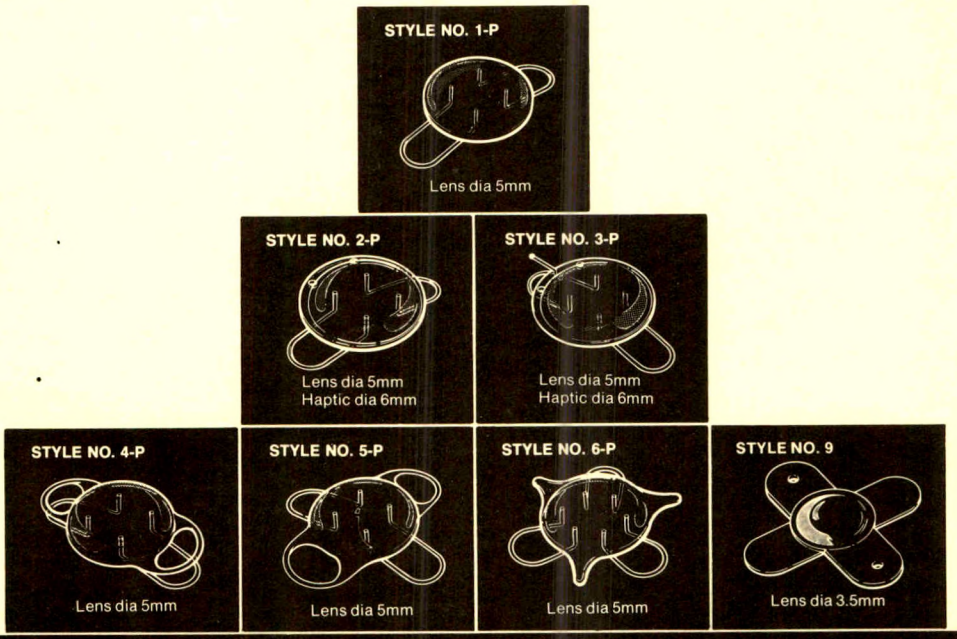
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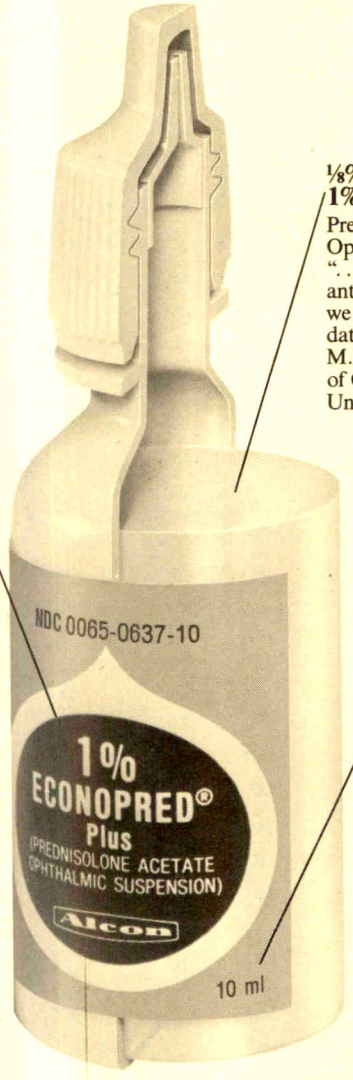
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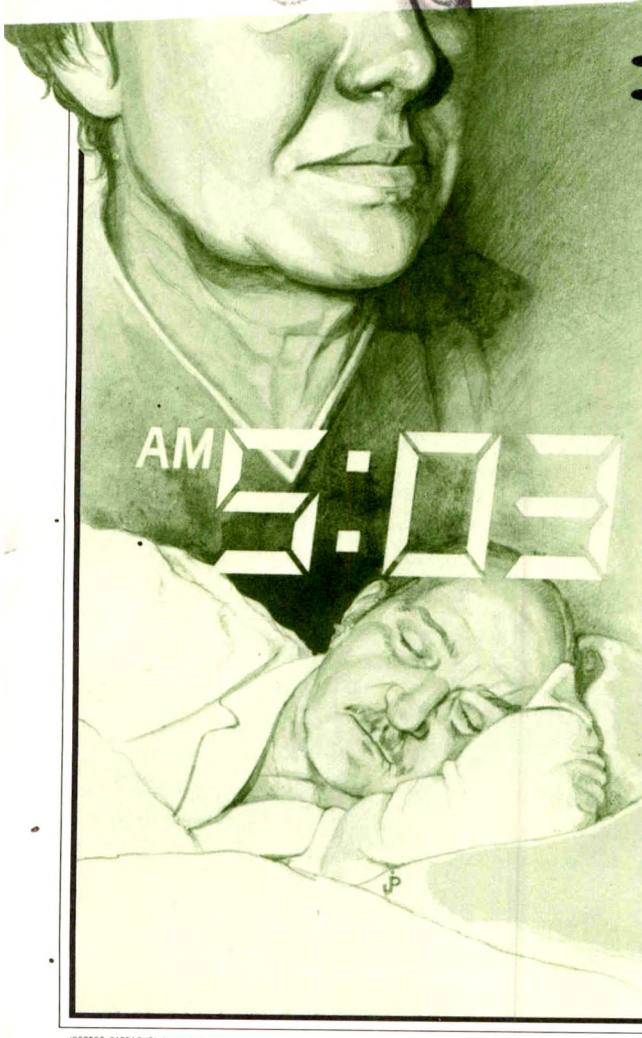
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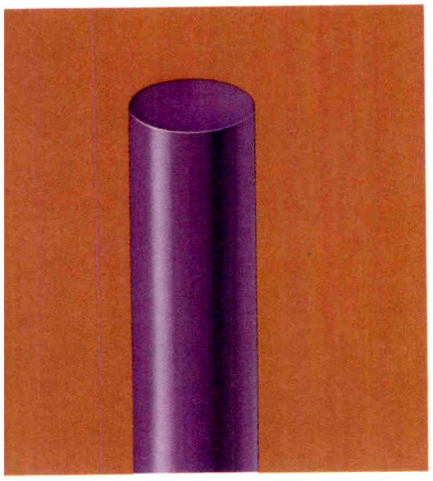
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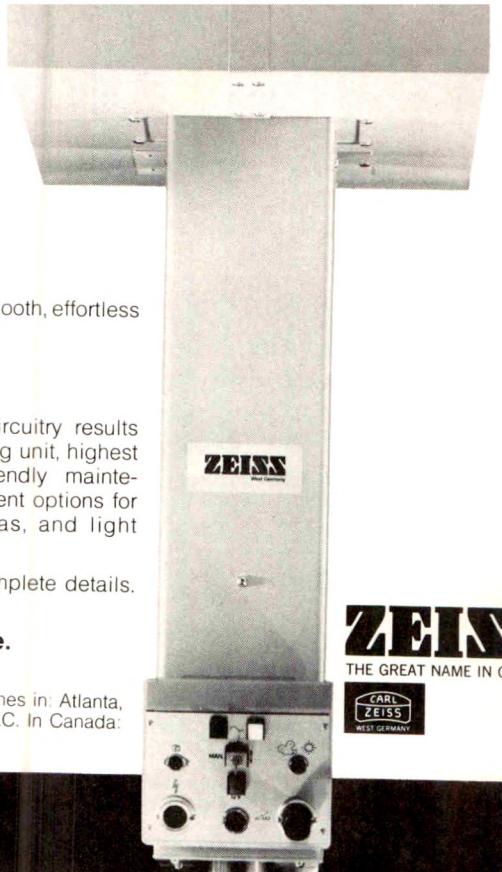
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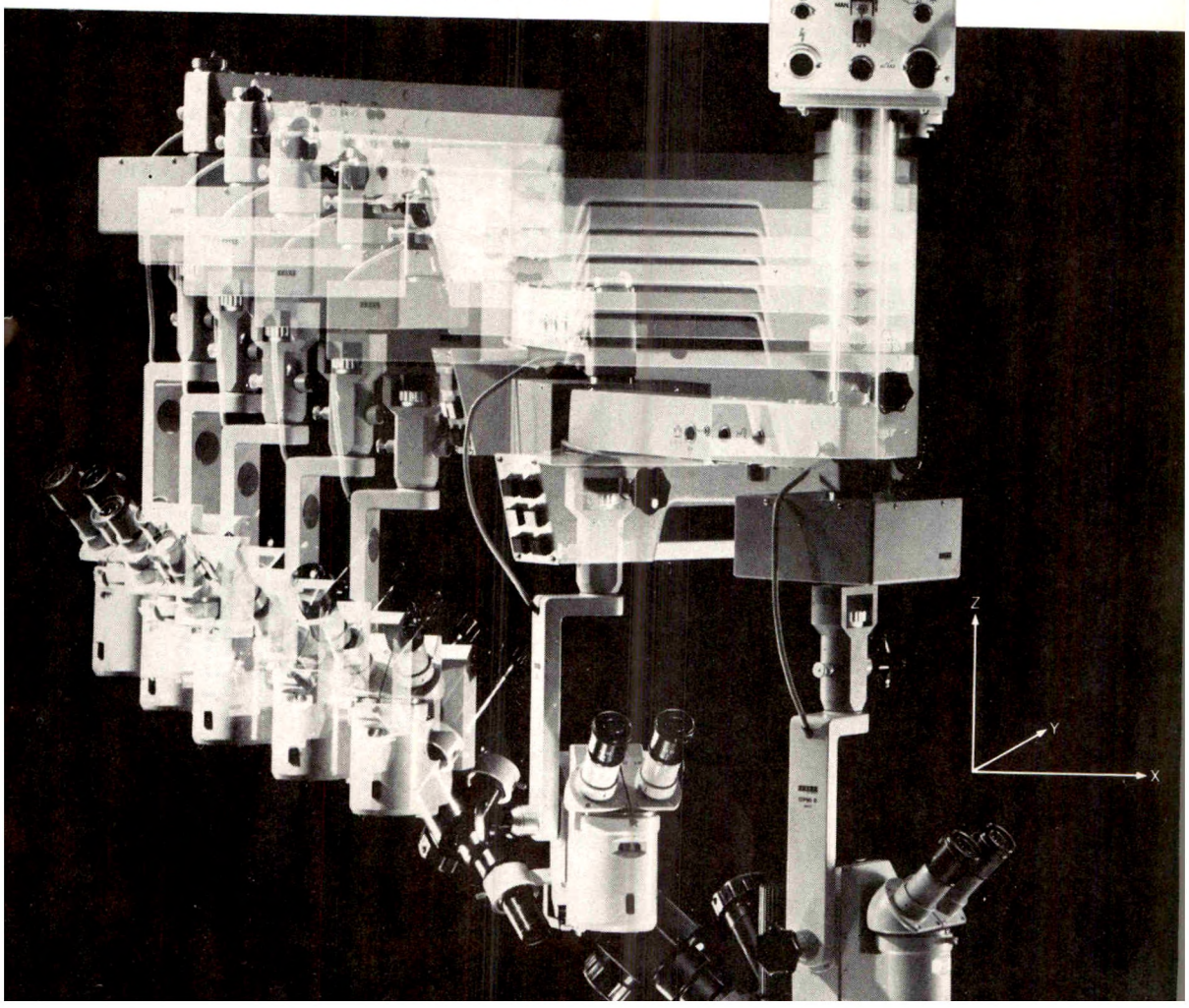
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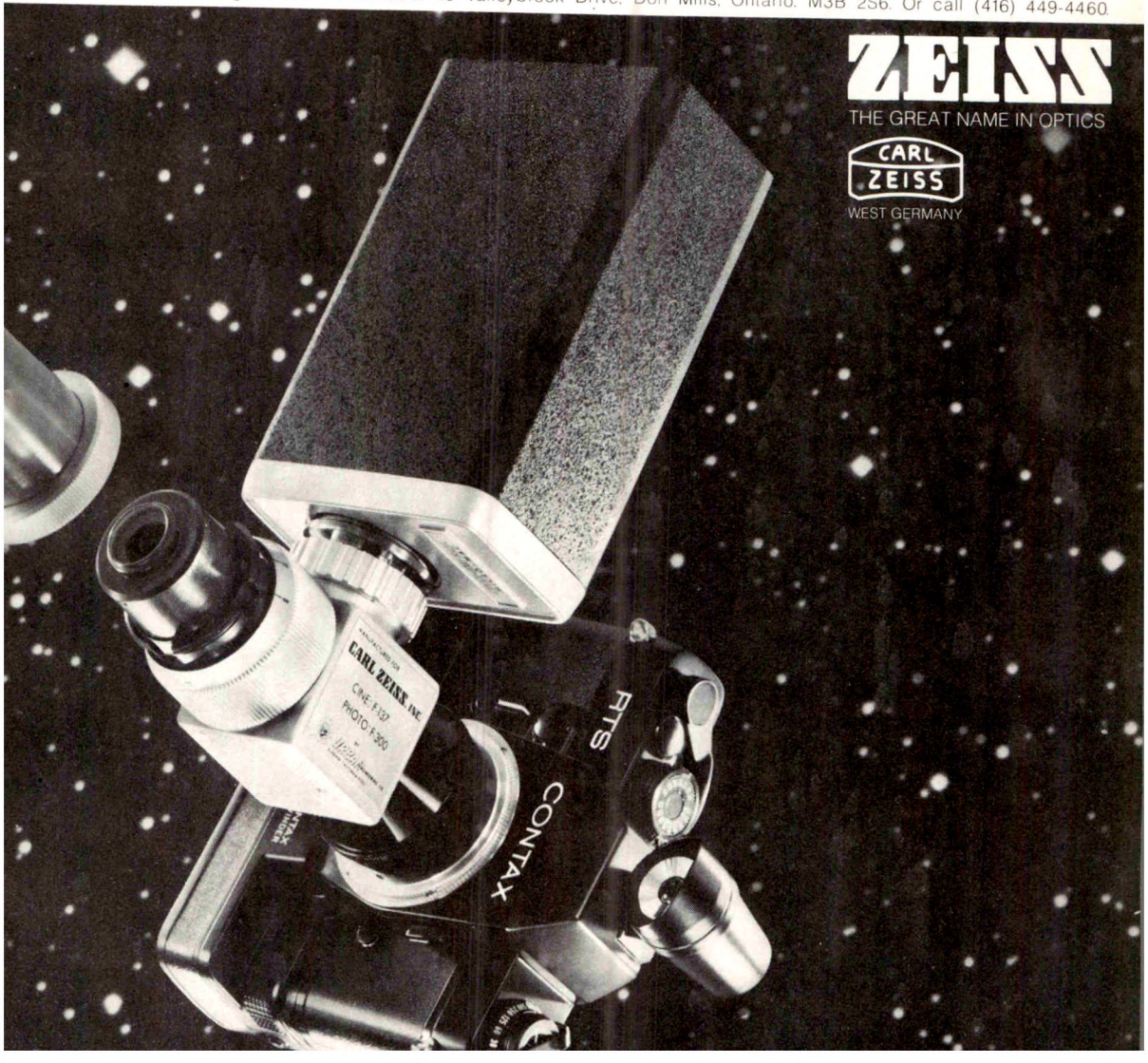
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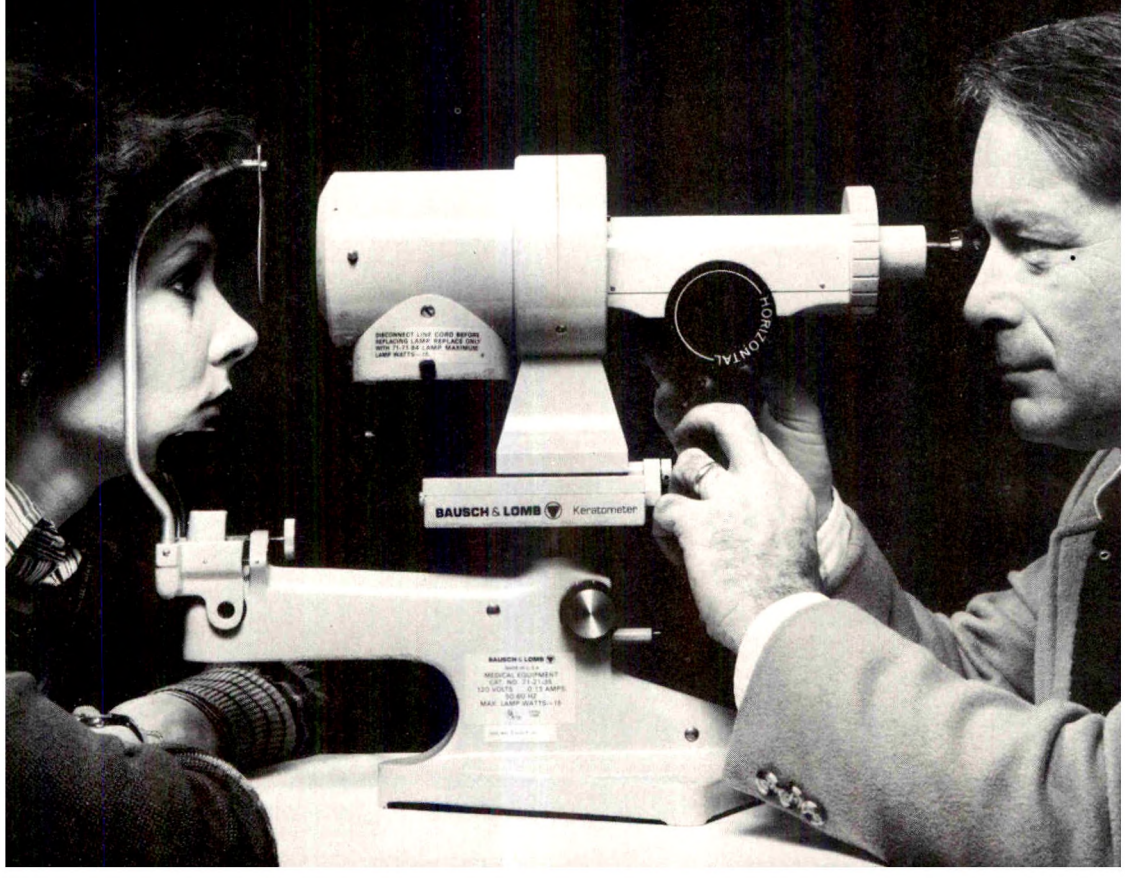
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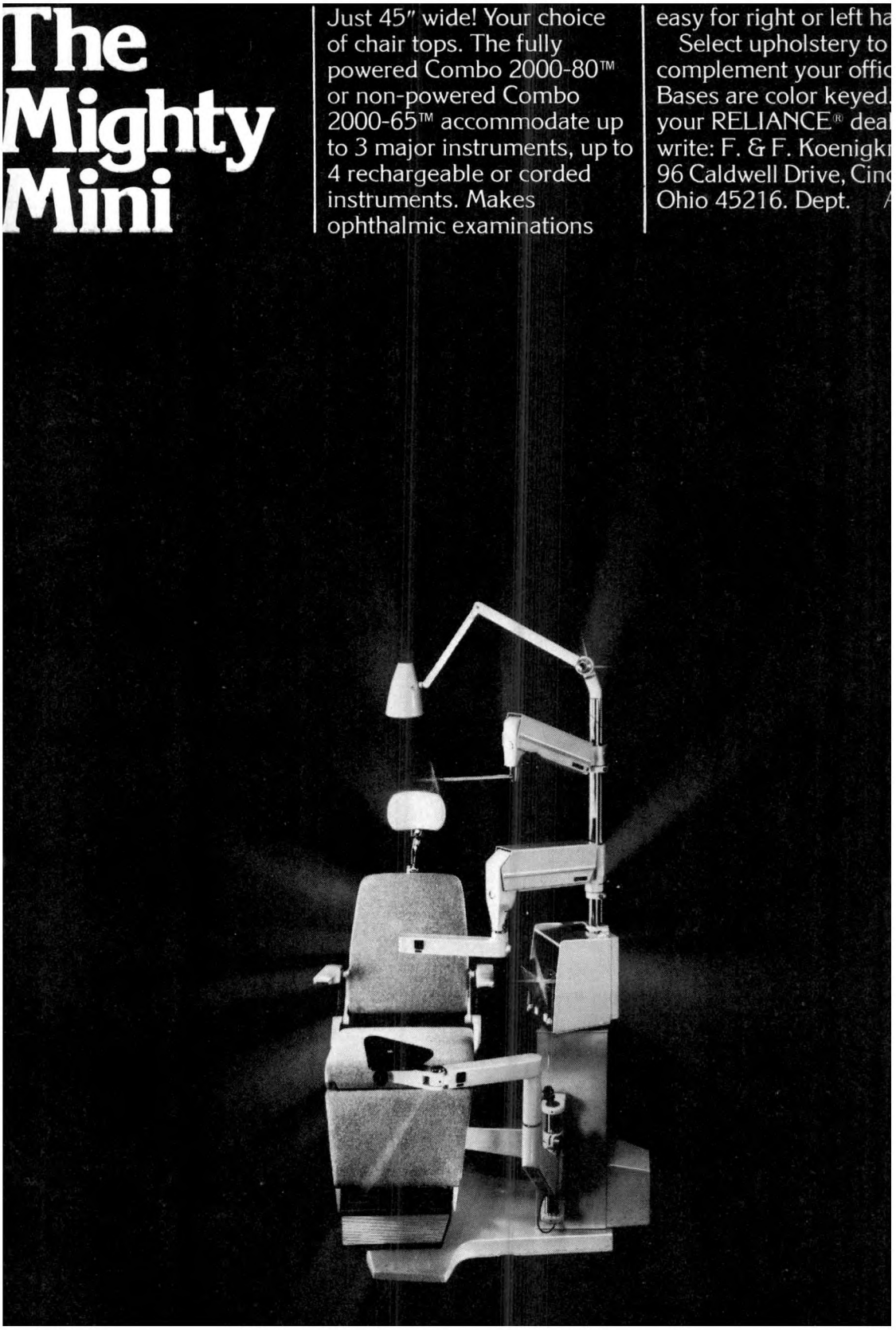
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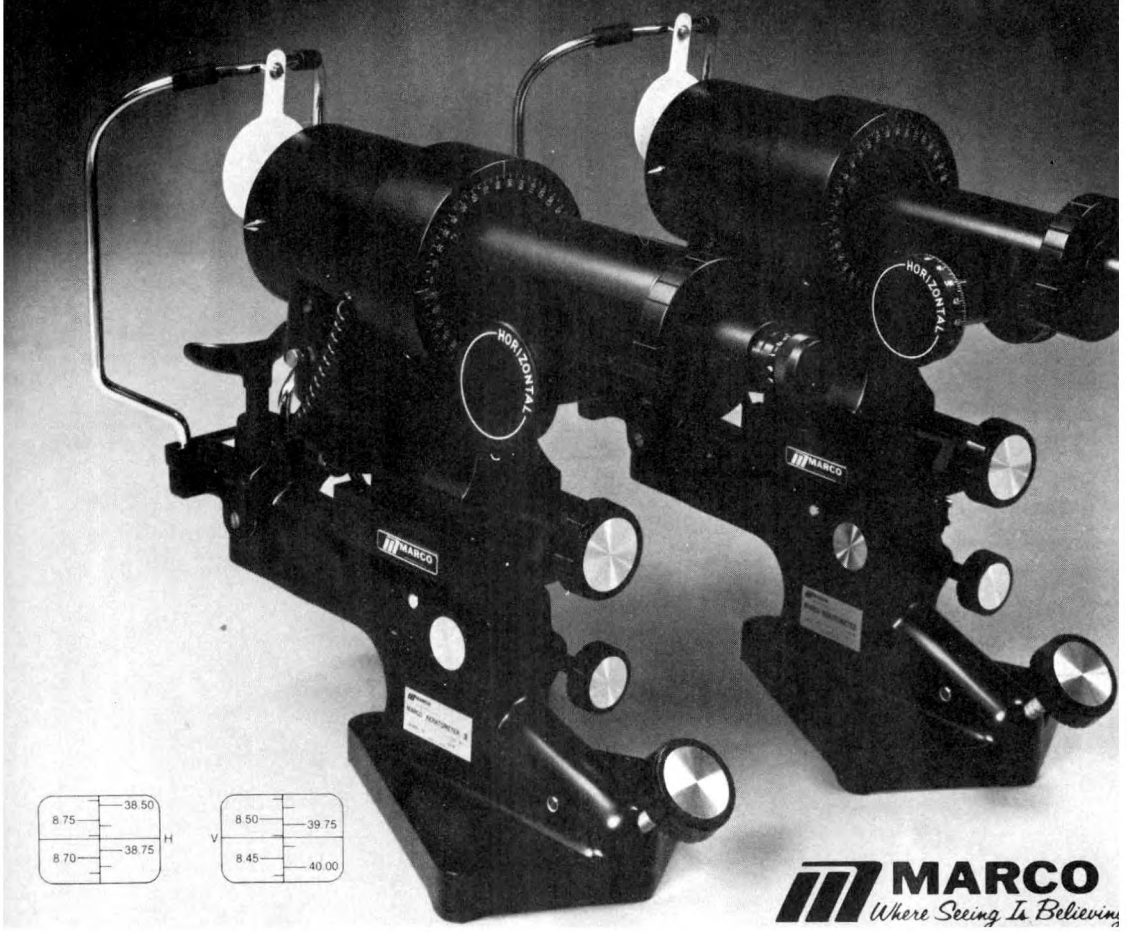
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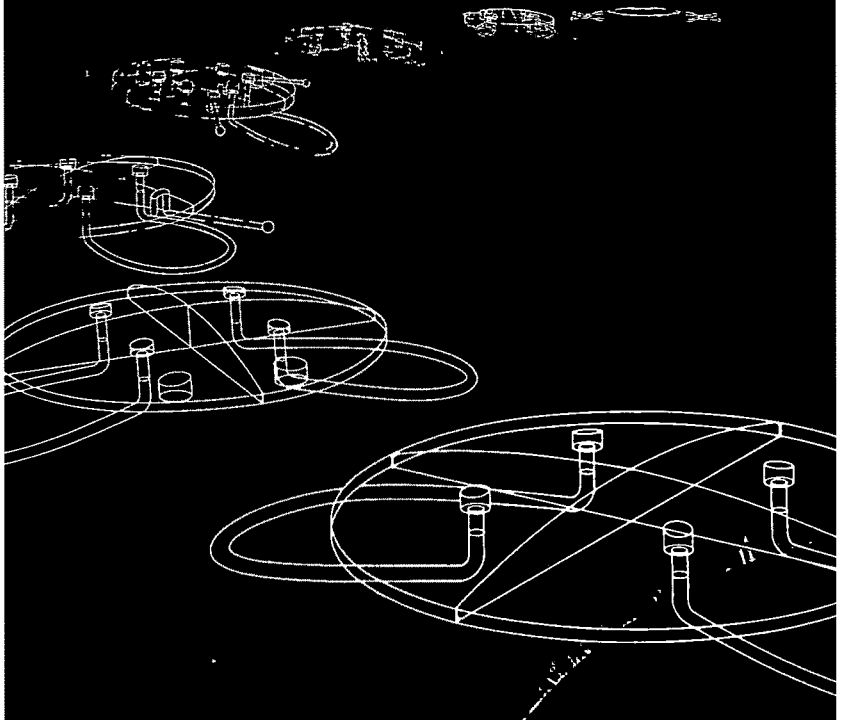
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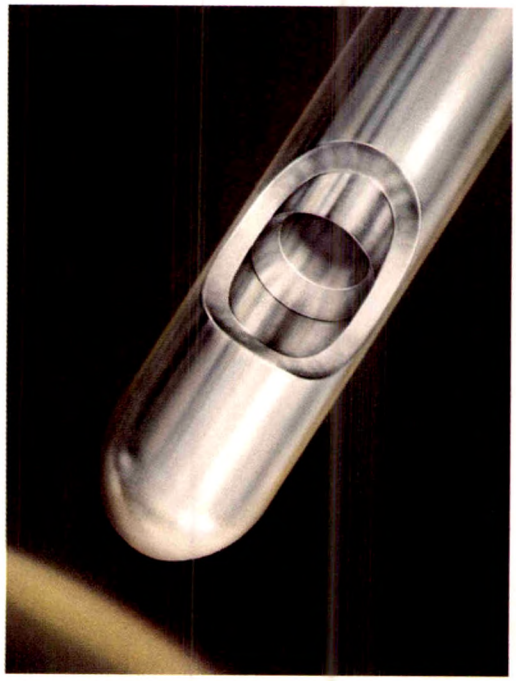
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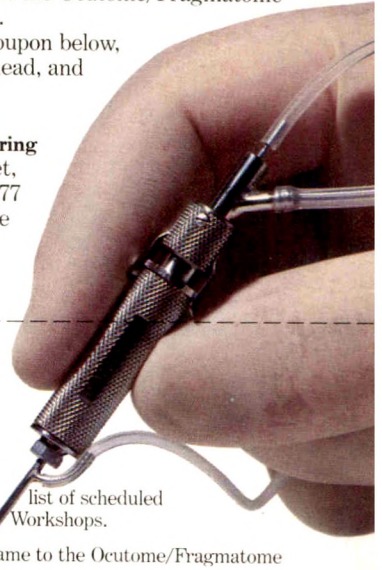
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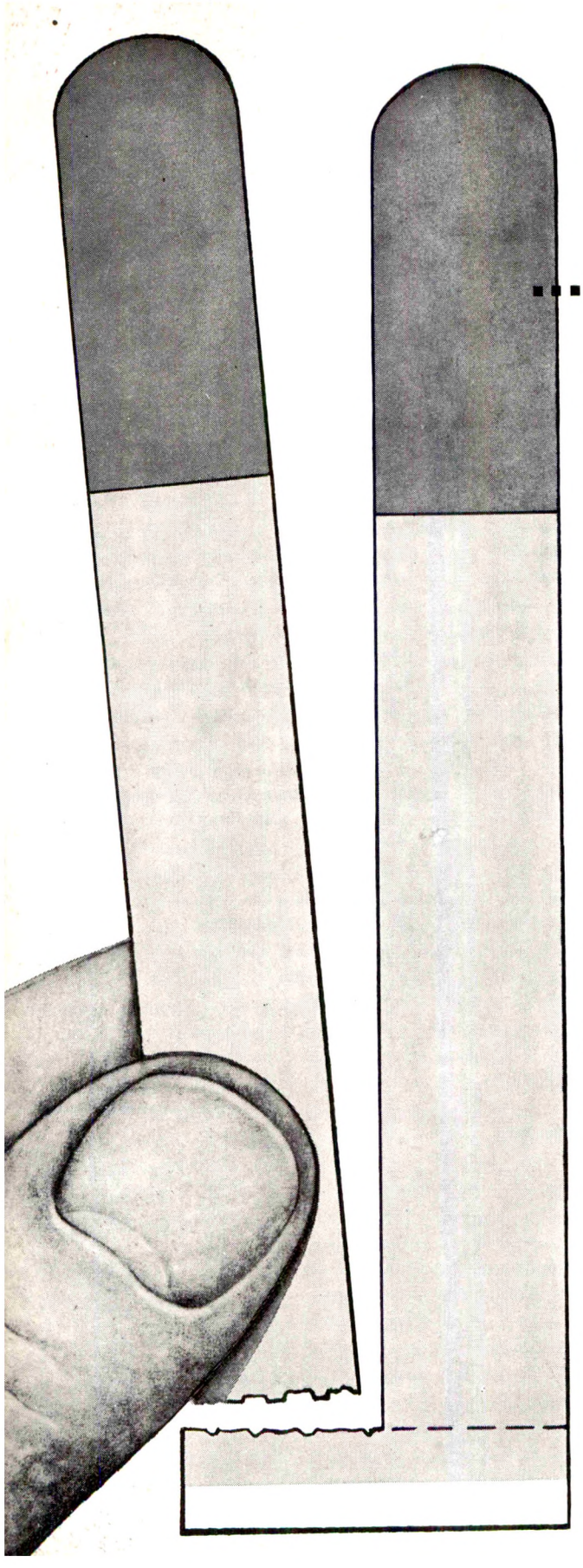


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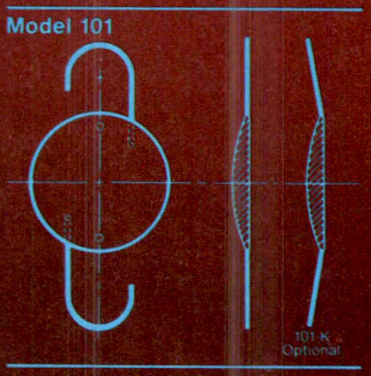
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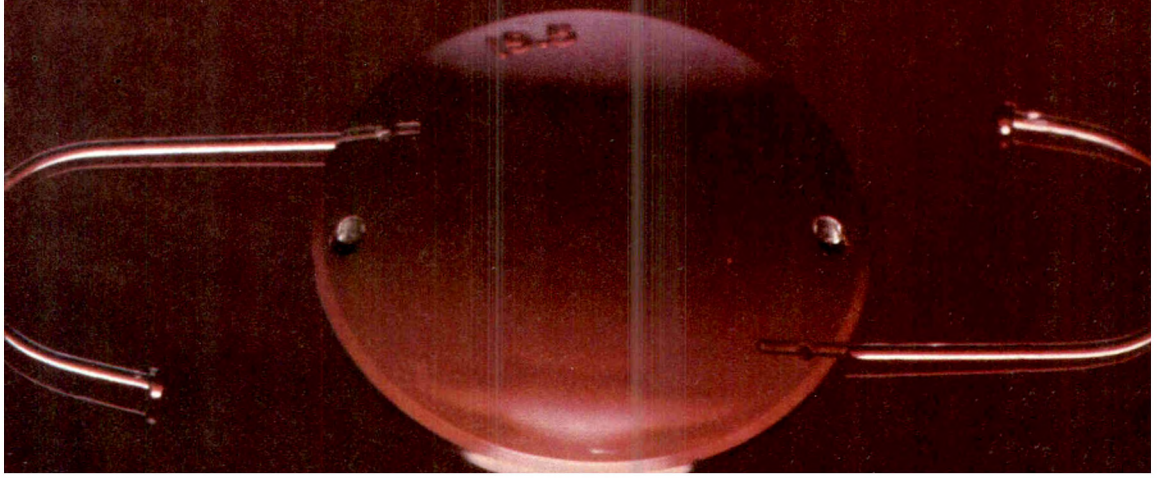
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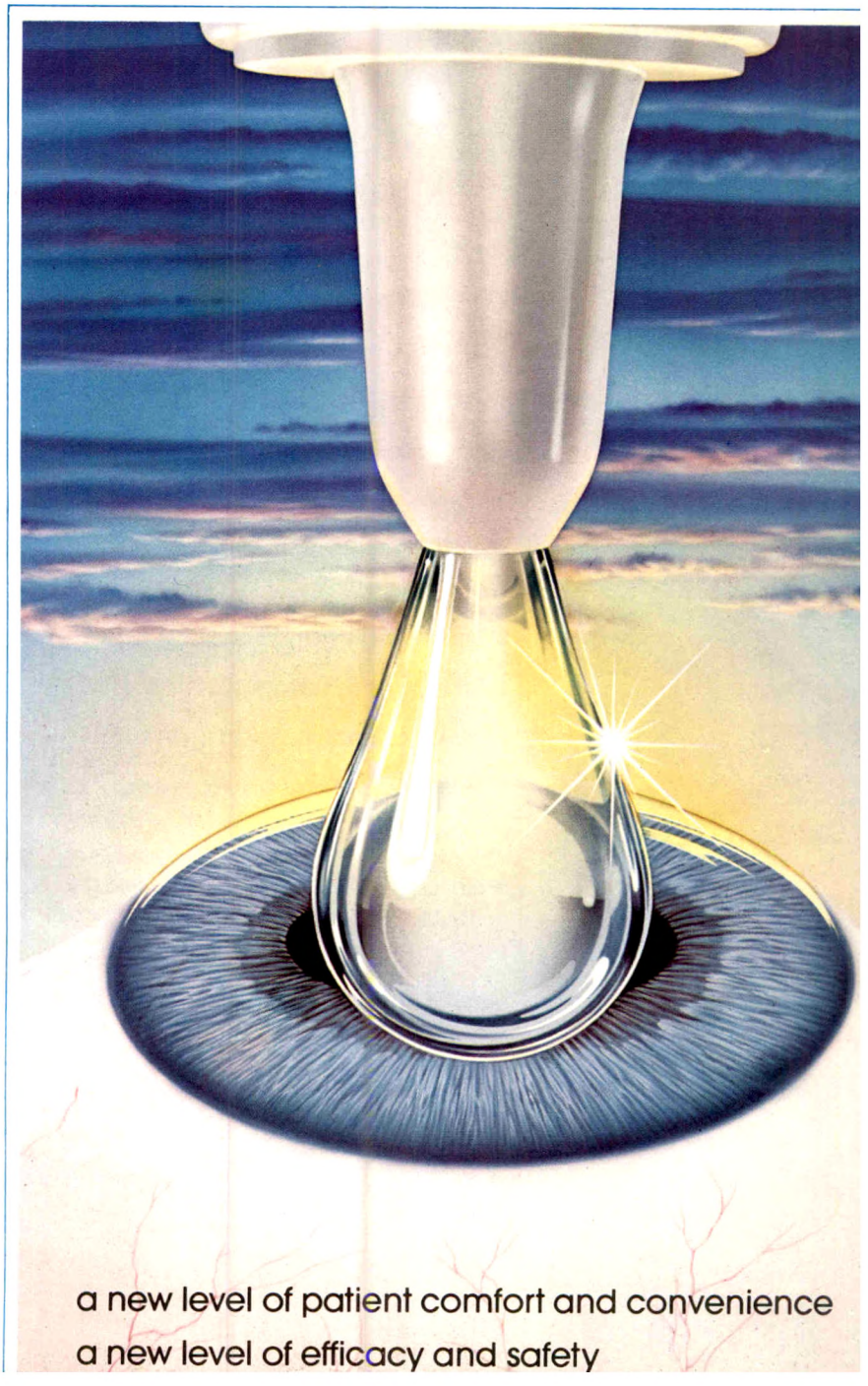
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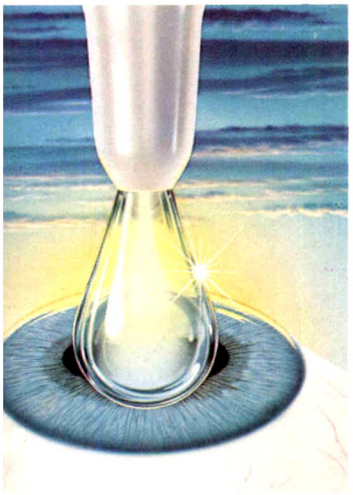


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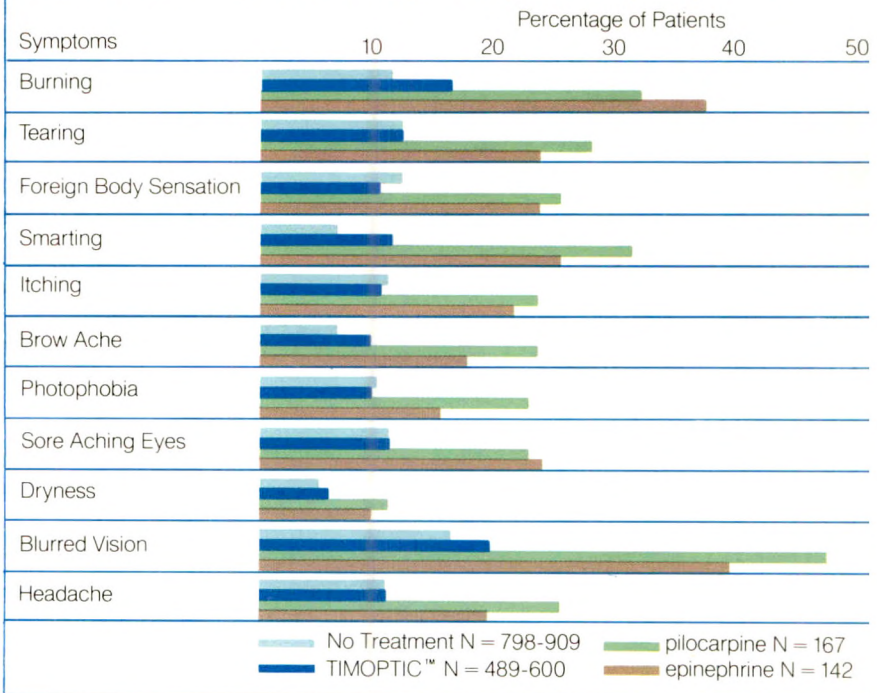
Sufficient clinical data have not been obtained to show safety or efficacy in narrow-angle or angle-closure glaucoma.

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a new level of patient comfort and convenience



In clinical studies—a much lower incidence of ocular discomfort than with pilocarpine or epinephrine



Adverse effects commonly caused by pilocarpine and epinephrine as reported in the literature—rarely encountered with TIMOPTIC™ (Timolol Maleate, MSD)

Drug-Induced Adverse Effects

pilocarpine	TIMOPTIC™ (in clinical studies)	epinephrine	TIMOPTIC™ (in clinical studies)
extreme miosis	none reported	conjunctival irritation	rare
spasm of accommodation	none reported	hyperemia	rare and mild
shallowing of the anterior chamber	none reported	macular edema in aphakic patients	none reported
night blindness and dimming of vision	none reported	pigment deposits on lid margins and conjunctiva	none reported
ciliary and conjunctival congestion	rare and mild		

With TIMOPTIC,™ slight reduction of the resting heart rate has been observed in some patients. Local hypersensitivity reactions have occurred rarely.

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new Timoptic™

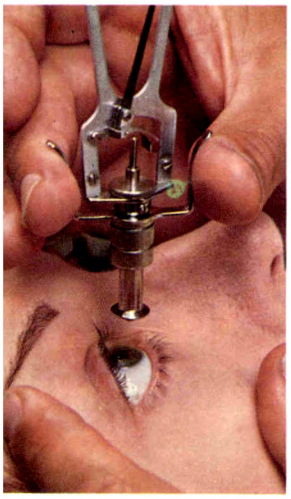
(TIMOLOL MALEATE | MSD) OPHTHALMIC SOLUTION

a beta-adrenergic blocking agent in ophthalmic solution...for reduction of elevated IOP in chronic open-angle glaucoma

- Fast onset of action (usually within ½ hour)
- Based on clinical studies of 638 patients maintained on therapy from 14 to 477 days:
  approximately 76% (485 of 638) of patients satisfactor managed (IOP less than 22 mm Hg) on TIMOPTIC™ alone
  approximately 93% (593 of 638) of patients satisfacto managed with TIMOPTIC™ alone or administered concomitantly with other antiglaucoma agents
- No evidence of diminished responsiveness reported in 102 patients treated for at least two years
- Absence of miosis may facilitate visualization of optic disc and evaluation of visual fields
- Usually well tolerated
- Produced fewer and less severe side effects than either pilocarpine or epinephrine

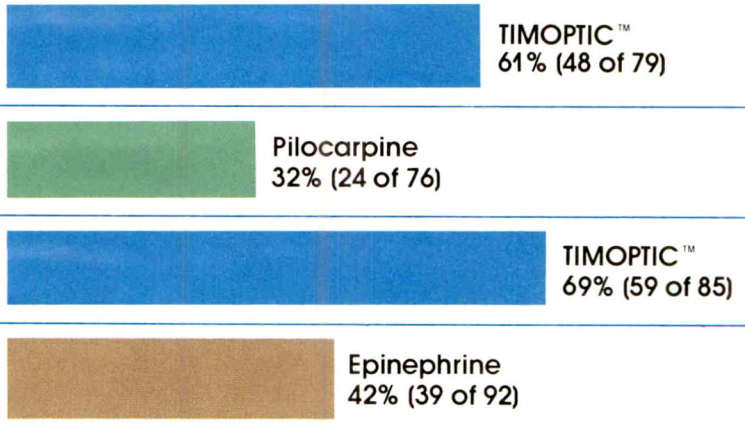
TIMOPTIC™ should be used with caution in patients with known contraindications to systemic use of beta-adrenergic receptor blocking agents. Patients who are already receiving a beta-adrenergic blocking agent orally should be observed for a potential additive effect.

a new level of efficacy and safety



In comparative clinical studies—significantly more effective than pilocarpine or epinephrine

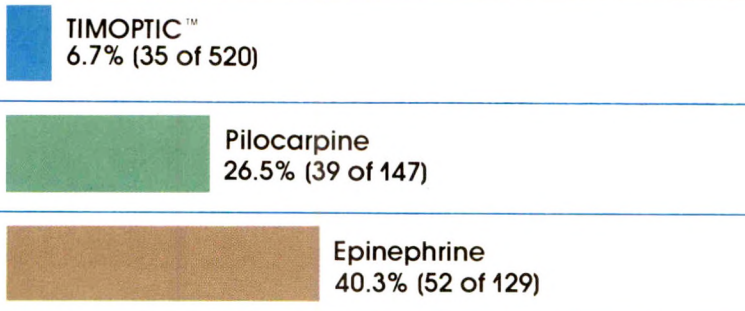
In multiclinic studies, TIMOPTIC™ (Timolol Maleate, MSD) reduced IOP in proportionately more patients



% of patients with IOP reduced to less than 22 mm Hg ($p<0.01$)

Data are derived from the final visit (week 17) in the multiclinic pilocarpine and epinephrine comparative studies. These include patients who withdrew due to ineffective response or an adverse clinical experience.

In all clinical studies, therapy with TIMOPTIC™ resulted in fewer dropouts* than with pilocarpine or epinephrine

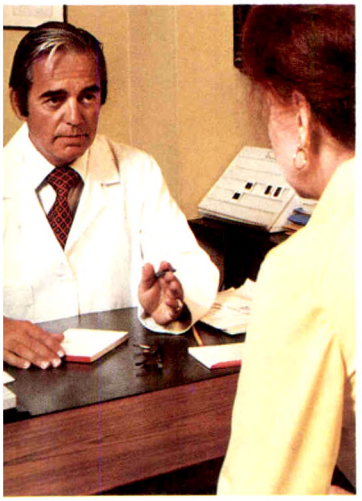


Data include patients participating in clinical studies lasting 14 to 477 days.

*Dropouts are defined as patients whose IOP could not be reduced to levels below 22 mm Hg, or those who withdrew because of an adverse clinical experience.

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new Timoptic™

(TIMOLOL MALEATE | MSD) OPHTHALMIC SOLUTION

significantly broadens the medical options in antiglaucoma therapy

- **Permits prolonged maintenance therapy—no evidence of tolerance reported** In a clinical study of 102 patients treated for at least two years, there was no evidence of diminished responsiveness to TIMOPTIC™.
- **Compatible with other agents** Concomitant therapy with pilocarpine and other miotics, and/or epinephrine, and/or systemica administered carbonic anhydrase inhibitors, such as acetazolamide, can be instituted for the patient who needs reduction of IOP greater than provided by one drop of 0.5% TIMOPTIC™ twice a day. Dosages above one drop of 0.5% TIMOPTIC™ twice a day generally have not been shown to produce further reduction in intraocular pressure.
- **Helpful in the medical management of a broader range of patients** In some patients who respond inadequately to maximum available drug therapy, the addition of TIMOPTIC™ may result in satisfactory management of intraocular pressure, thus possibly postponing the need for surgery.
- **Often effective in patients previously difficult to manage**...such as working patients incapacitated by accommodat spasm produced by miotics, older patients with cataracts whose vision is impaired with miotics, patients with heavily pigmented irides whose response to pilocarpine is diminished, and aphakic patients who may develop macular edema from epinephrine.

Since clinical studies in children have not been done, TIMOPTIC™ is not recommended for use in children at this time. TIMOPTIC™ has no been studied in human pregnancy. The use of TIMOPTIC™ in pregnant women requires that the anticipated benefits be weighed against the possible hazards.

a beta-adrenergic blocking agent in ophthalmic solution...for reduction of elevated IOP in chronic open-angle glaucoma



Dosage Guidelines:

How to transfer from current therapy to TIMOPTIC™ (Timolol Maleate, MSD):

1 On the first day: continue with the agent(s) already being used and add one drop 0.25% TIMOPTIC™ in each eye b.i.d.

2 On the second day: discontinue the previously used agent(s) and continue with TIMOPTIC™ in each eye b.i.d.

How to add TIMOPTIC™ to other agents:

1 Administer one drop 0.25% TIMOPTIC™ in each eye b.i.d....while continuing with the agent(s) already being used.

2 If a higher dosage of TIMOPTIC™ is required, substitute one drop 0.5% TIMOPTIC™ in each eye b.i.d....while continuing with the agent(s) already being used.

How to start patients on TIMOPTIC™:

Usual starting dosage:
one drop 0.25% TIMOPTIC™
in each eye twice a day.



If clinical response is not adequate:

Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC™ twice a day in each eye. If the intraocular pressure is maintained at satisfactory levels, the dosage schedules may be changed to one drop once a day in each eye. Dosages above one drop of 0.5% TIMOPTIC™ twice a day generally have not been shown to produce further reduction in IOP.

Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

In patients with a history of severe cardiac disease, pulse rates should be checked.

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For a brief summary of Prescribing Information, please see following page.

for many patients—a significant advance for the reduction of elevated IOP

- in chronic open-angle glaucoma
- in ocular hypertension
- in aphakic glaucoma
- in some patients with secondary glaucoma

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11. Zimmerman, T. and Kaufman, H.: Timolol: Dose response and duration of action, Arch. Ophthalmol. *95(4)*:605-607, April 1977.

CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients who are hypersensitive any component of this product.

PRECAUTIONS: Should be used with caution in patients with known contraindications to systemic use of beta-adrenergic receptor blocking agents. These include bronchial asthma; sinus bradycardia and greater than first-degree block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure; concomitant use wit adrenergic-augmenting psychotropic drugs. In patients with a history of severe cardiac disease, pulse rates should be checked. Patients who are already receiving a beta-adrener blocking agent orally and who are given TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta b

Sufficient clinical data have not been obtained to show safety or efficacy in narrow-angle angle-closure glaucoma.

Pregnancy: TIMOPTIC has not been studied in human pregnancy. The use of TIMOPTIC in pregnant women requires that the anticipated benefit be weighed against possible hazards.

Use in Children: Since clinical studies in children have not been done, TIMOPTIC is not recommended for use in children at this time.

ADVERSE REACTIONS: Occasionally, signs and symptoms of mild ocular irritation have been reported. Slight reduction of the resting heart rate (mean reduction 2.9 beats/minute, standard deviation 10.2) has been observed in some patients. Local hypersensitivity reactio have occurred rarely.

Note: TIMOPTIC has been used in patients with glaucoma wearing conventional (PMMA) hard contact lenses, and has generally been well tolerated. TIMOPTIC has not been studie patients wearing lenses made with materials other than PMMA.

HOW SUPPLIED:

TIMOPTIC Ophthalmic Solution, 0.25%
TIMOPTIC Ophthalmic Solution, 0.5%
Both are available in 5-ml plastic OCUMETER® Ophthalmic Dispenser with a controlled dro

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For more detailed information, consult your MSD Representative or see full Prescribing Infc

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ON

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References: 1. Data on file, Alcon Laboratories, Inc. 2. Lemp, M.A., Design and Development of an Artificial Tear. Scientific Exhibit, AAOO Annual Meeting, Dallas, Tex., 1975.

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Contraindications: 1. Active uveal inflammation.
2. Most cases of angle-closure glaucoma, due to the possi of increasing angle block.
3. Hypersensitivity to the active or inactive ingredients.
Warnings: 1. *Use in Pregnancy.* Safe use of anticholinesterat medications during pregnancy has not been established; no has the absence of adverse effects on the fetus or on the res tion of the neonate.
2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patie receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.
3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same tim undergoing treatment with systemic anticholinesterase med tions for myasthenia gravis, because of possible adverse ad effects.
Precautions: 1. Gonioscopy is recommended prior to initiati of therapy.
2. Where there is a quiescent uveitis or a history of this cor tion, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.
3. While systemic effects are infrequent, proper use of the requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.
4. Temporary discontinuance of medication is necessary i salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregula occur.
5. Patients receiving PHOSPHOLINE IODIDE who are ex posed to carbamate or organophosphate type insecticides a pesticides (professional gardeners, farmers, workers in plan manufacturing or formulating such products, etc.) should b warned of the additive systemic effects possible from absorp of the pesticide through the respiratory tract or skin. During periods of exposure to such pesticides, the wearing of respir masks, and frequent washing and clothing changes may be advisable.
6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchia asthma, spastic gastrointestinal disturbances, peptic ulcer, p nounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that r respond adversely to vagotonic effects.
7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.
8. PHOSPHOLINE IODIDE (echothiophate iodide) should used with great caution, if at all, where there is a prior history retinal detachment.
Adverse Reactions: 1. Although the relationship, if any, of re detachment to the administration of PHOSPHOLINE IODID has not been established, retinal detachment has been repo in a few cases during the use of PHOSPHOLINE IODIDE in patients without a previous history of this disorder.
2. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia visual blurring may occur.
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5. Prolonged use may cause conjunctival thickening, obst tion of nasolacrimal canals.
6. Lens opacities occurring in patients under treatment fo glaucoma with PHOSPHOLINE IODIDE have been reporte and similar changes have been produced experimentally in normal monkeys. Routine examinations should accompany clinical use of the drug.
7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by pres ing a sympathomimetic mydriatic such as phenylephrine.
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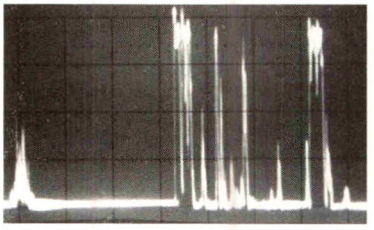
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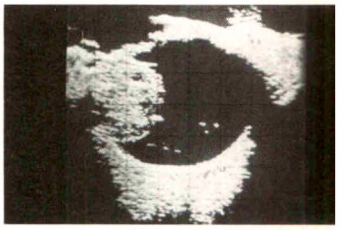
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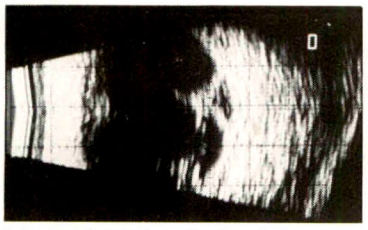
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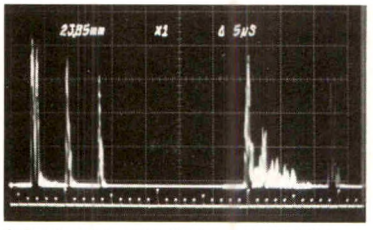
1. *A-scan* of tumor of the ciliary body showing attenuation pattern of a malignant melanoma.



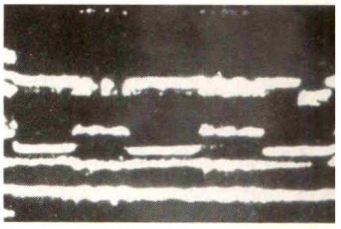
2. Immersion *B-scan* of the same melanoma with posterior vitreous hemorrhage.



3. Contact *B-scan* through a closed lid shows distinctive "X" shape of vitreous membranes and traction retinal detachment in diabetic retinopathy.

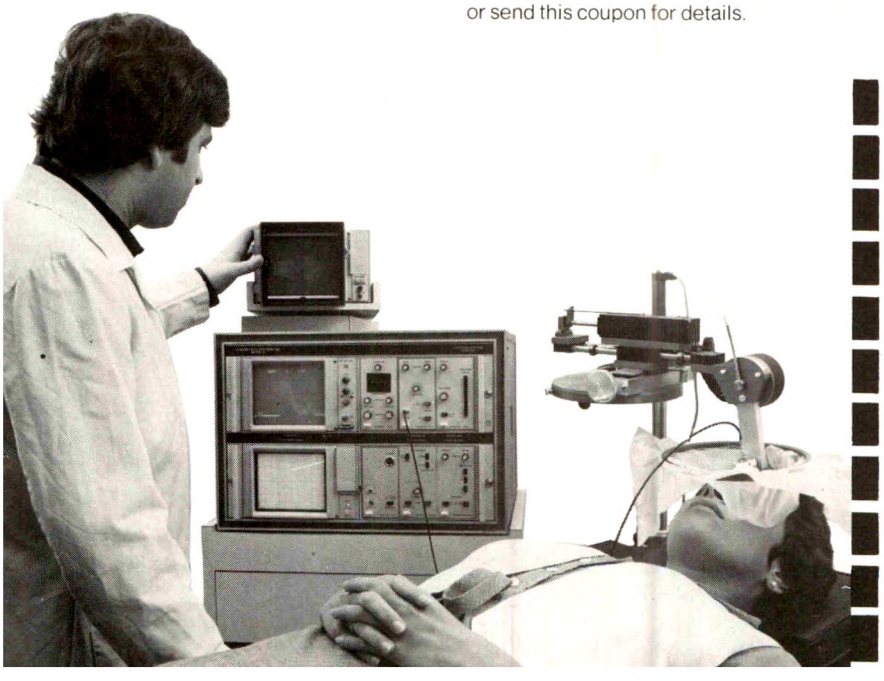


4. Ophthalmoscan oscilloscope presentation showing characteristic A-scan pattern along the visual axis and simultaneous readout of axial length in millimeters.



5. Magnified M-scan of the posterior segmen of the globe showing arterio-venous pulsations.

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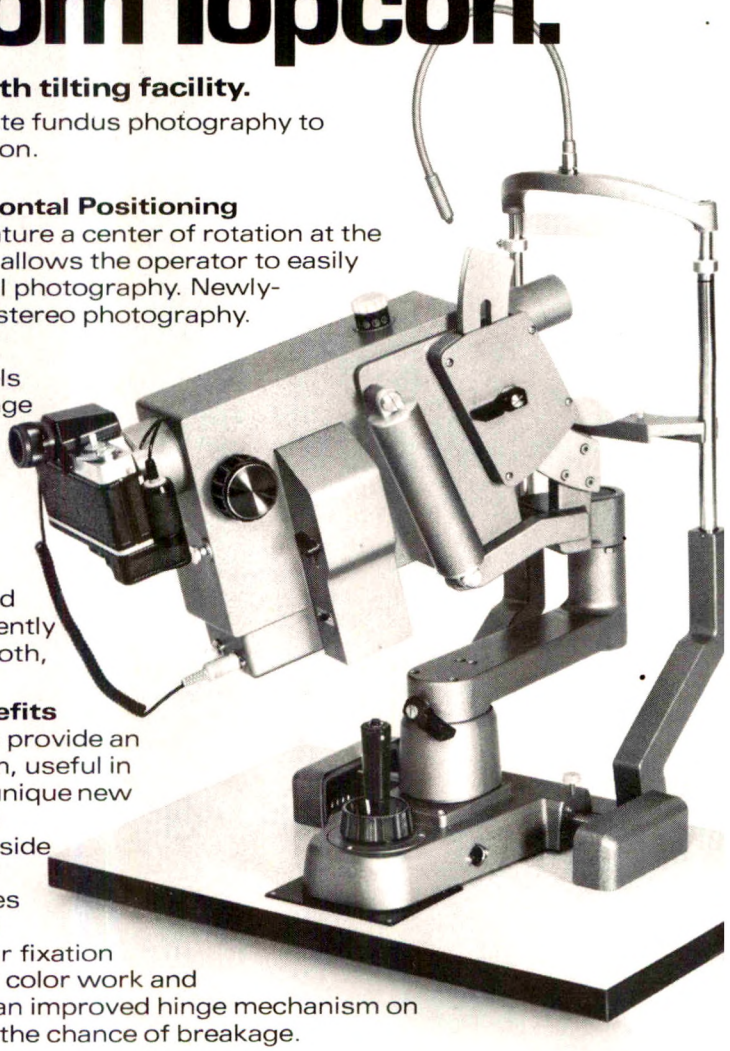
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Robert Machemer, M.D., Miami, Florida
Richard C. Troutman, M.D., New York, New York

Otolaryngology Speakers:
Thomas C. Calcaterra, M.D., Los Angeles, California
Michael E. Glasscock, M.D., Nashville, Tennessee
Charles J. Krause, M.D., Iowa City, Iowa
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CLINICAL APPLICATIONS OF NEW DIAGNOSTIC PROCEDURES

March 8, 9, 10, 1979

Anatole Hotel • Dallas, Texas

PURPOSE

The multitude of new ophthalmological diagnostic tests now available is a source of great confusion to many practitioners. The goal of this program is to present a meeting which will explain these tests as simply as possible and suggest a logical approach to their utilization.

FACULTY

Eliot Berson, M.D., Boston
Alan Bird, M.D., London
Frederick Blodi, M.D., Iowa City
Peter Bringewald, M.D., Dallas
Devron Char, M.D., San Francisco
Steven Charles, M.D., Memphis
D. Jackson Coleman, M.D., New York
Edward Cotlier, M.D., New Haven
Victor Curtin, M.D., Miami
Gary Fish, M.D., Dallas
H. MacKenzie Freeman, M.D., Boston
Dwain Fuller, M.D., Dallas
William Hutton, M.D., Dallas
John R. Lynn, M.D., Dallas
Ronald Michels, M.D., Baltimore
Karl Ossoinig, M.D., Iowa City
John Sheets, M.D., Odessa
William Snyder, M.D., Dallas
Richard Srebro, M.D., Dallas
Gerald Tennant, M.D., Dallas
Albert Vaiser, M.D., Dallas
George Weinstein, M.D., San Antonio
Lorenz Zimmerman, M.D., Washington, D.C.

TOPICS

Presurgical Evaluation of Eyes with Cataracts and Other Opaque Media: ultrasonography, bright-flash electroretinography, visually evoked potential, laser interferometry, standard retinal function tests

Tumor Evaluation and Management: fluorescein angiography, ^{32}P, ultrasonography, tumor skin testing, aqueous enzymology, enucleation—pros and cons

Diagnosis and Management of Hereditary Fundus Disease: electroretinography, electro-oculography, dark adaptation, visually evoked potential, fluorescein angiography, genetic counseling, metabolic concepts

PROGRAM DIRECTORS

Doctors Vaiser, Snyder, Hutton and Fuller

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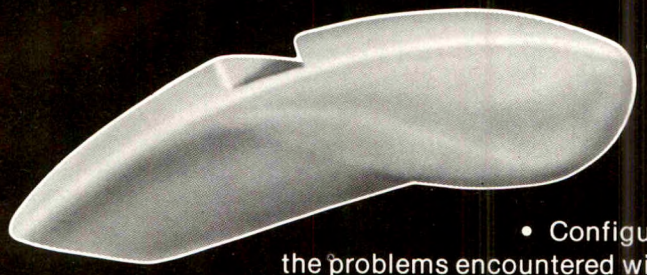
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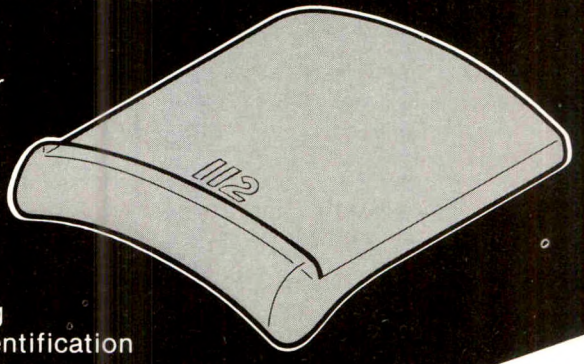


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* The Fishmouth Phenomenon II. Wedge Scleral Buckling, Arch. Ophthalmol. Vol. 95: 1782-1787, Oct. 1977.

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May 16-19, 1979

OBJECTIVES:
An in-depth symposium to provide the practicing and resident surgeon with an Oculoplastic Course featuring LIVE SURGERY VIDEO TAPES, FILMS, LECTURES AND PARTICIPANT'S CADAVER SURGERY.

FACULTY:
I. Baras, M. D.
L. Bergmann, M. D.
B. Cosman, M. D.
N. Cousins, Esq.
M. Dunn, M. D.
D. Gaffin, Esq.
H. Gould, M. D.
M. Guibor, C. O.
P. Guibor, M. D.
S. Hecht, M. D.
L. Herman, PhD.
A. Messina, M. D.
E. Wiggs, M. D.
D. Wolfley, M. D.
and others.

SUBJECTS:
Cosmetic Blepharoplasty, Blepharoptosis, Trauma Surgery, Lid Reconstruction, Lacrimal Surgery, Orbital Reconstruction, Entropion, Ectropion, Orbital Fractures and Orbital Tumors.

VII NERVE SURGICAL DISSECTION COURSE

(25 HRS. CME & CAT I)

May 20-22, 1979

OBJECTIVES:
A unique and practical surgical course, presented by multiple disciplines, covering the management of FACIAL PALSY and FACIAL SPASM, featuring PARTICIPANT'S CADAVER SURGERY.

FACULTY:
L. Bergmann, M. D.
J. Conley, M. D.
M. Dunn, M. D.
F. Gillen, M. D.
P. Guibor, M. D.
J. Hagedoorn, Ph.D.
P. Janetta, M. D.
M. May, M. D.
A. Messina, M. D.
S. Parisier, M. D.
J. Smith, M. D.
D. Wolfley, M. D.
D. Zorub, M. D.

SUBJECTS:
Facial Nerve Testing, Dynamic-Static Techniques, Lid Spring, Silicone Encircling, Facial Reconstruction, Direct Nerve Repair and Grafting, 12-7 Hook-up Animation, Neuromuscular Pedicle Transfer and Nerve Avulsion.

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OCULOPLASTIC COURSE
May 16-19, 1979

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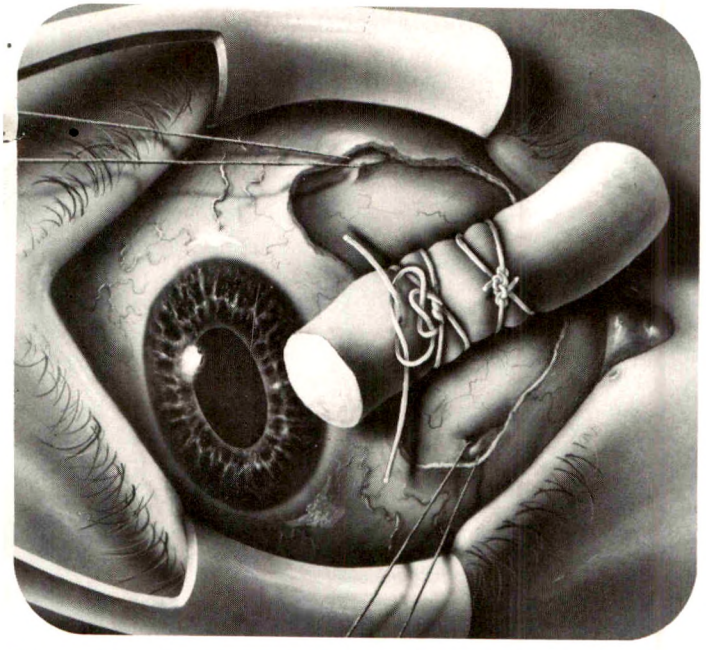
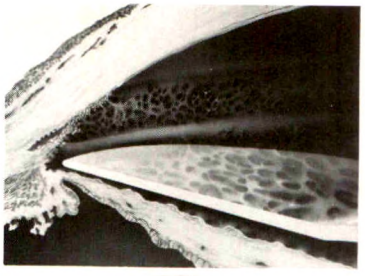
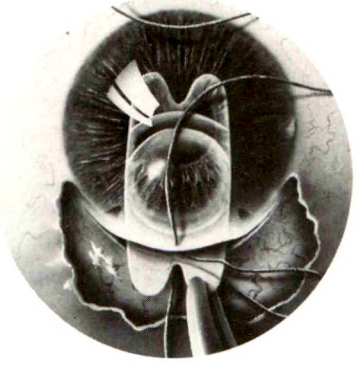
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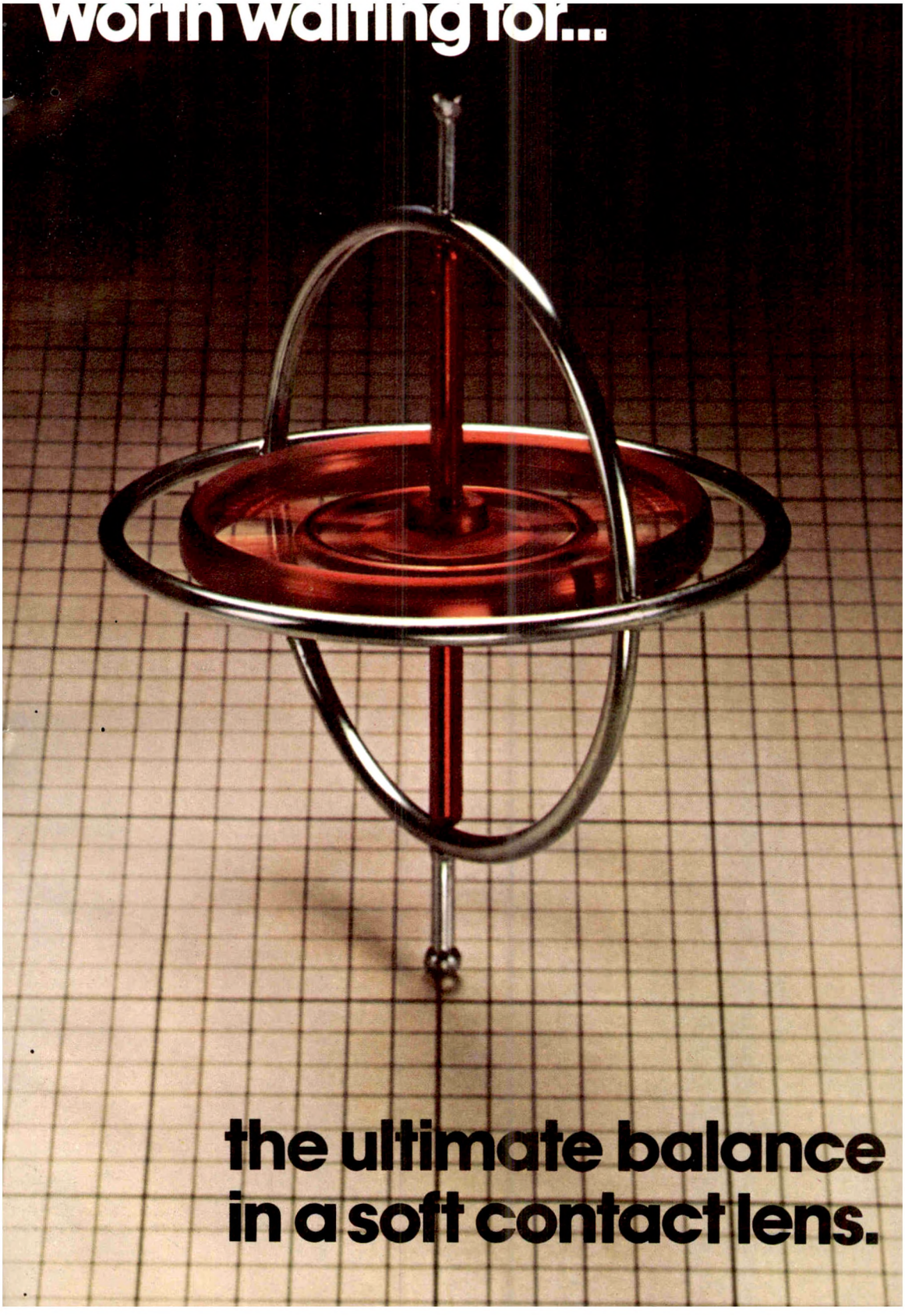
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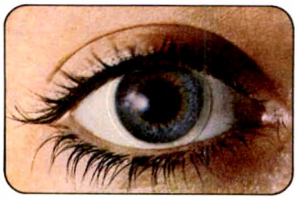

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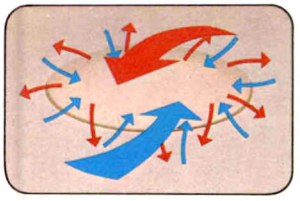

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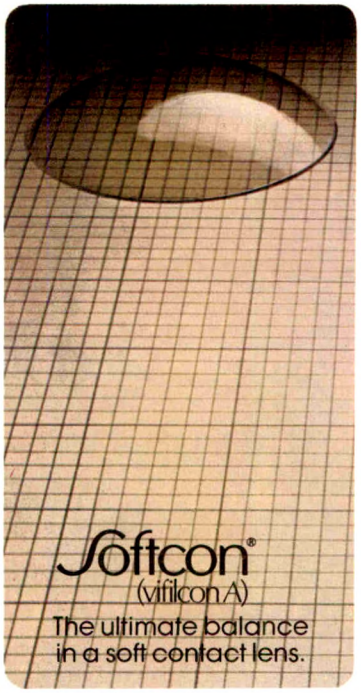
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DESCRIPTION The SOFTCON (vifilcon A) Contact Lens is a hemispherical flexible transparent shell which covers the cornea and part of the sclera. The lens is composed of vifilcon A, a soft hydrophilic plastic co-polymer of 2-hydroxyethyl methacrylate and povidone, USP. The chemical name is: Poly (2-hydroxyethyl methacrylate-co-ethylene dimethacrylate-co-methacrylic acid-g-povidone). When fully hydrated, the lens contains about 55% water by weight.

INDICATIONS The SOFTCON Contact Lens is indicated for the correction of visual acuity in persons with non-diseased eyes and in aphakia. It is indicated for persons who have spherical ametropias, refractive astigmatism usually 1.50 diopters or less and/or corneal astigmatism of 2.00 diopters or less.

CONTRAINDICATIONS Presence of any active infection or inflammation of the eye, insufficient tears, corneal hypoesthesia or any systemic disease which may affect the eye adversely or be exaggerated by wearing contact lenses.

WARNINGS Medications and Eye Drops—The SOFTCON Contact Lens must be stored only in FLEXSOL® soaking solution. **NEVER USE CONVENTIONAL HARD CONTACT LENS PRODUCTS WITH THE SOFTCON CONTACT LENS.** No ophthalmic solutions or medications may be used by SOFTCON Contact Lens wearers immediately prior to or during wear of the lens. No solutions other than PREFLEX®, FLEXSOL, and NORMOL® used for cleaning and chemical disinfection may be used.

Aphakic Patients—Patients who have undergone surgery for cataract removal should not be fitted with SOFTCON Contact Lenses during the immediate post-operative period, until, in the opinion of the surgeon, the eye has healed completely.

Abrasions and Infections—If a lens becomes less comfortable to the wearer than when it was first placed on the cornea, the lens should be removed immediately, and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present, or any abnormal eye condition is observed concurrently with lens wear, the lens should be removed immediately and a clinician must be consulted.

Lens Care—WEARERS MUST ADHERE TO THE RECOMMENDED DAILY CLEANING, CARE AND DISINFECTION REGIMEN AS DESCRIBED IN THE SOFTCON WEARER'S BOOKLET. FAILURE TO ADHERE TO THE RECOMMENDED PROCEDURES MAY RESULT IN THE DEVELOPMENT OF SERIOUS EYE INFECTION.

Wearing Restriction—The lens should be removed before sleeping or swimming, and should not be worn in the presence of irritating fumes or vapors.

Visual Blurring—If unusual visual blurring occurs, the lenses must be removed until the condition subsides. If blurring persists see your eye care practitioner.

PRECAUTIONS Storage—The SOFTCON Contact Lenses must be stored only in FLEXSOL soaking solution. If left exposed to air, the lenses will dehydrate, becoming hard and easily damaged. If a lens dehydrates, it should be carefully handled and soaked again in FLEXSOL until it returns to its normal soft, supple state.

Cleaning and Disinfection—THE SOFTCON CONTACT LENS MUST BE BOTH CLEANED AND DISINFECTED DAILY. ONE PROCEDURE DOES NOT REPLACE THE OTHER.

Cleaning—Daily cleaning is necessary to remove mucus and other deposits which may have accumulated on the lens surface from normal ocular secretions, airborne debris, or handling. The lenses must be cleaned before being disinfected, as deposits on the lens tend to harden and become more difficult to remove after the lenses are disinfected.

Disinfection—Lenses must be disinfected daily according to the chemical disinfection regimen. For chemical disinfection, all three solutions, PREFLEX, FLEXSOL, and NORMOL, must be used and must be changed daily. In the event that the chemical disinfection materials are not available, the lenses should not be worn.

Hygiene—Hands must be washed, rinsed thoroughly and dried with a lint-free towel before handling the lenses. COSMETICS, lotions, soaps, oils and hand creams must not come in contact with the lenses since eye irritation may result. If aerosol sprays are used while the lenses are being worn, the eyes must be kept tightly closed until the sprays have settled.

Fluorescein—Use of fluorescein while the patient is wearing the lenses may cause the lenses to become discolored. Whenever fluorescein is used, irrigate the eyes with preserved normal saline solution, and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein irreversibly.

ADVERSE REACTIONS Serious corneal damage may result from wearing lenses which have been soaked in conventional (hard) contact lens solutions.

Eye irritation may occur within a short time after applying a hypertonic lens. Removal of the lens will relieve the irritation. Very rarely, a lens may adhere to an eye as a result of a patient sleeping with the lens on or while wearing a hypotonic lens. If a lens adheres for any reason, apply a few drops of ADAPETTES® directly to the eye and wait until the lens moves freely before removing it.

Clinical studies indicate that corneal edema as manifested by symptoms such as rainbows or halos around lights, or visual blurring may occur if lenses are worn for too long a time. Removal of the lenses and a rest period of at least one hour generally relieves these symptoms. If symptoms do not subside promptly, or if excess tearing, unusual secretions, or photophobia develop, professional consultation should be obtained.

DOSAGE AND ADMINISTRATION Fitting—Usual methods of fitting conventional (hard) contact lenses do not apply to the SOFTCON Contact Lens.

For a detailed description of the fitting technique, refer to the SOFTCON Fitting Booklet.

Wearing Schedule—The wearing schedule should be determined by the eye care practitioner. Studies have not been performed to support the safety of this lens for longer than the recommended wearing time.

Patients should wear their lenses for 8-16 hours on the day the lenses are dispensed. If patients cannot tolerate 16 hours of lens wear daily, the eyes should be examined and the lens fit re-evaluated.

Lens Care and Handling—Care must be taken on the initial visit to assure that the patient is supplied with a SOFTCON Care Kit and fully understands all proper care and handling procedures for the lenses. As with any contact lens patient, regular re-examination visits are necessary to assure ocular health and patient compliance with instructions.

How Supplied—Each lens is shipped sterile in a sealed glass vial containing buffered normal saline solution. The vial label is marked with the base curve, dioptric power, diameter and the manufacturing identification number of the lens.

Patient Care Kit—The SOFTCON Care Kit is a package required for cleaning, disinfection and storage of the lenses. It consists of the following:

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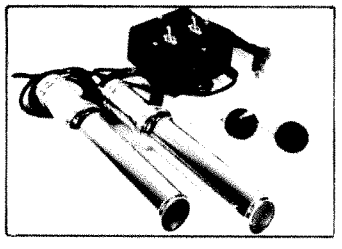
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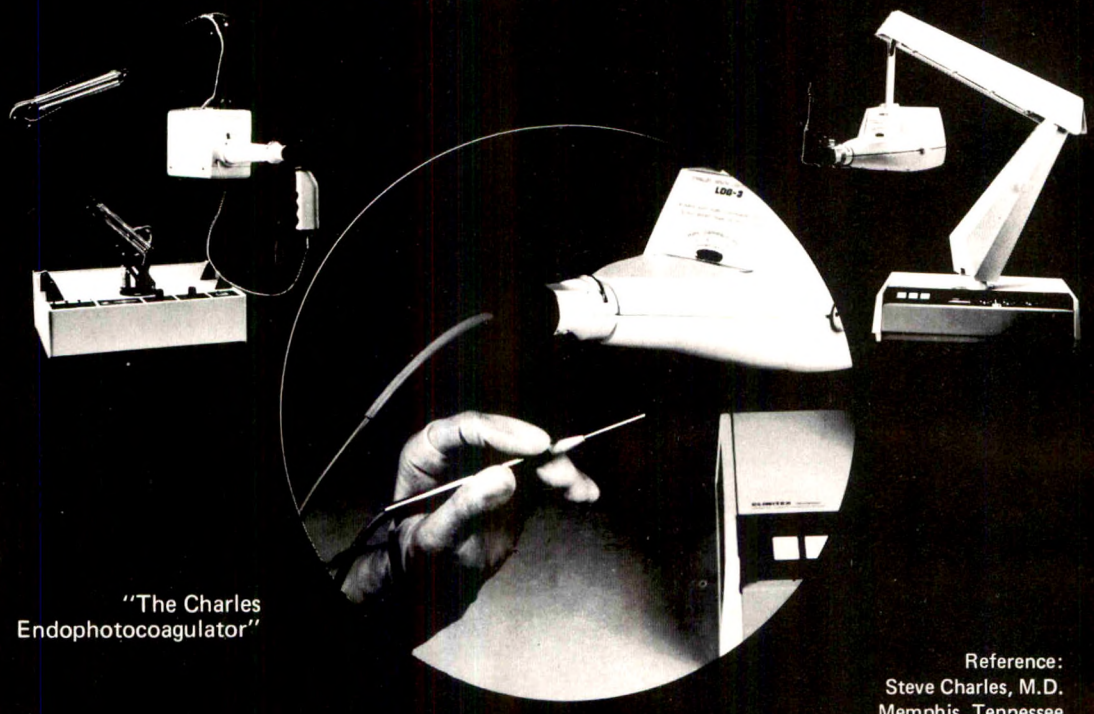
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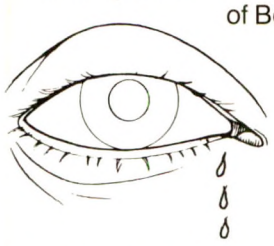
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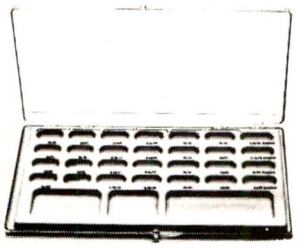
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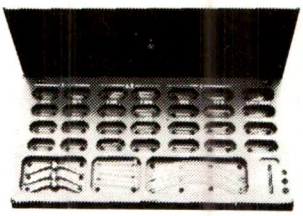
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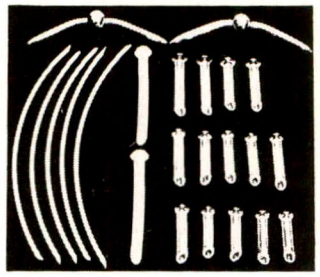
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* L.T. Jones M.D., Dacryocystorhinostomy, American Journal of Ophthalmology, Volume 59, No. 5, May, 1965.
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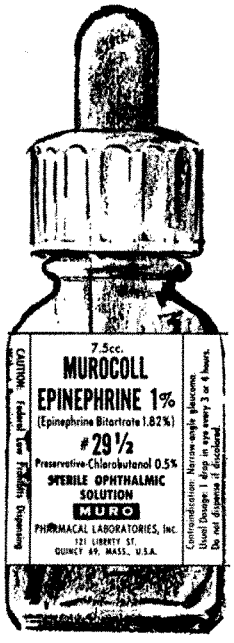
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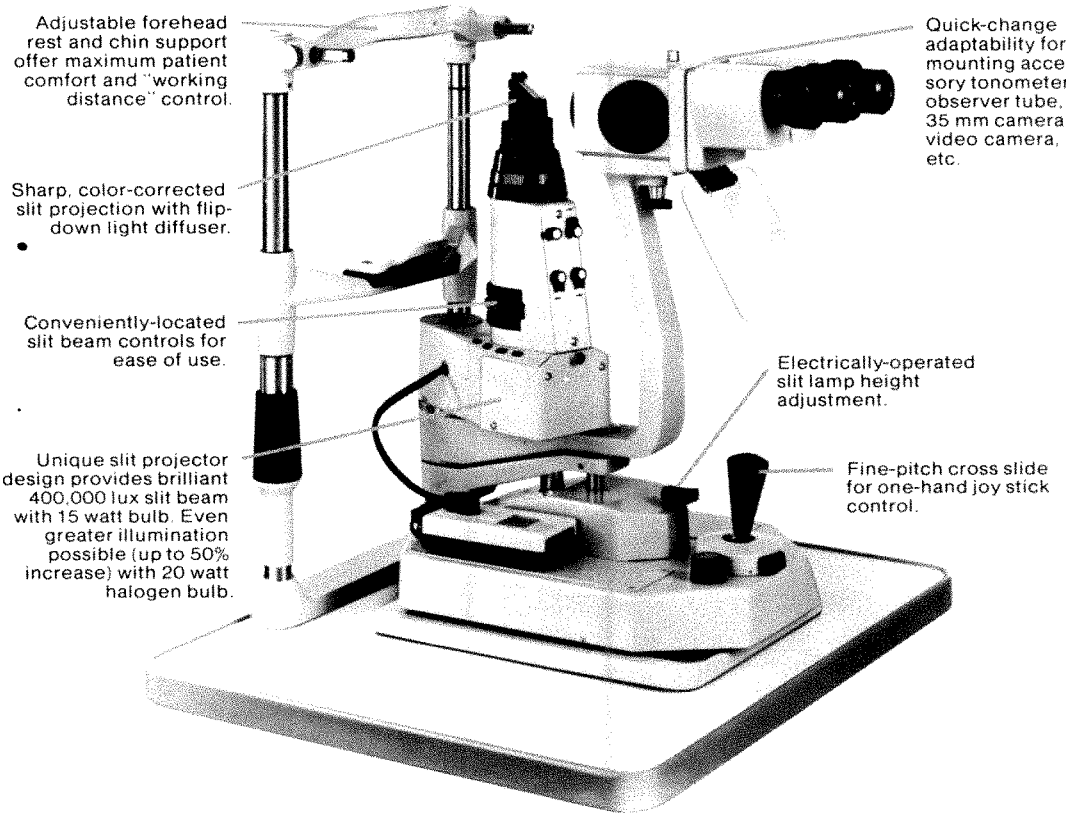
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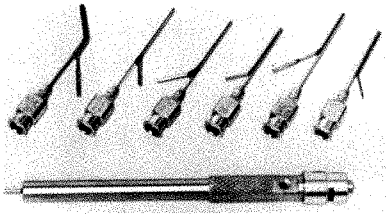
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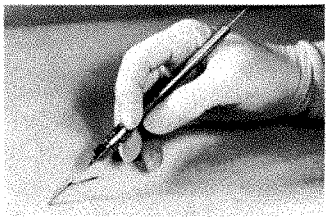
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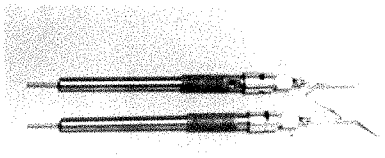
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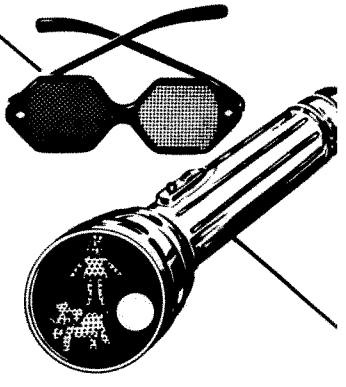






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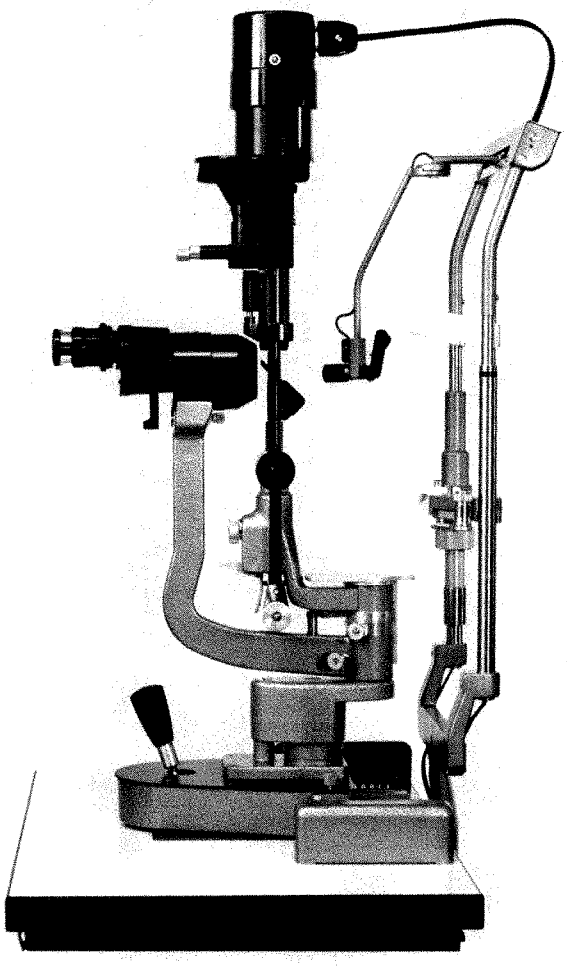
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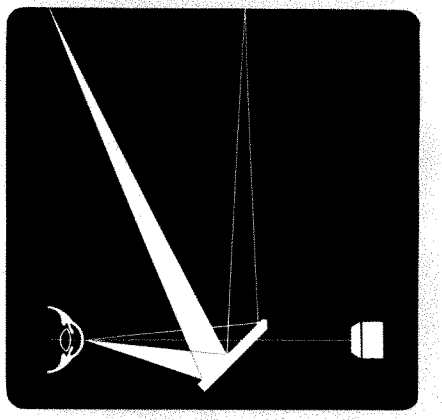
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This Seminar is designed to assist the practicing ophthalmologist in giving informed consent and rendering second opinions; to review the complications of cataract surgery, the problems of aphakia; to discuss newer methods to compensate for aphakia; review recent surgical techniques their indications, complications compared with "standard" intracapsular cataract extraction; review medical screening, anesthesia screening and "sitter" anesthesia

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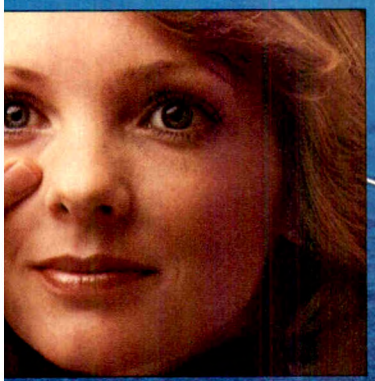
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(tetrafilcon A)
Hydrophilic Contact Lens



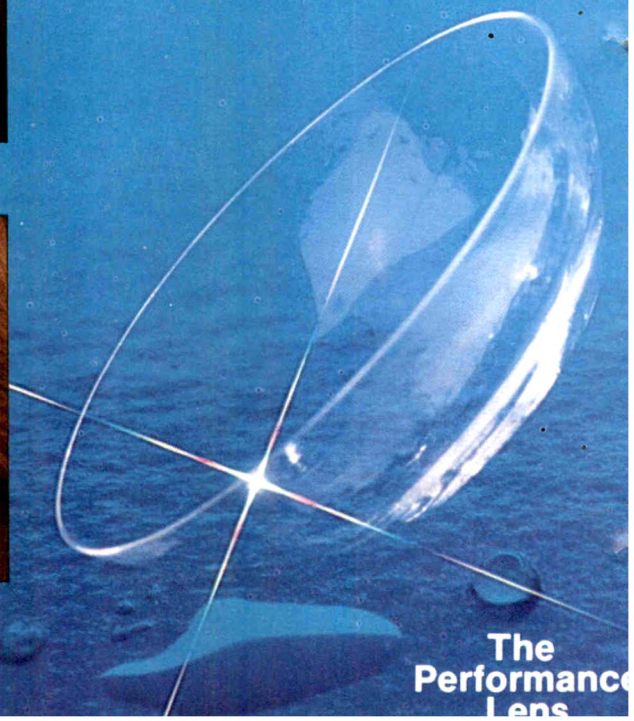
Outstanding Visual Acuity



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Predictable Fit



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utstanding Visual Acuity

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clinical study showed that over 96% of uaflex contact lens wearers achieved timum centration.[1] By centering so well, uaflex lenses virtually eliminate the induced tigmatism and lessened visual acuity sulting from decentered lenses.[2] Precise ntration helps in attaining a good fit with full rneal coverage and maximum visual acuity, ile permitting proper corneal respiration.

edictable Fit

complicated graphs, charts and lculations, because the Aquaflex "Vault" stem reduces fitting variables to just one... lens "Vault". Only 5 Vaults are needed to fit uaflex lenses;[3] and in clinical studies more an 90% of the patients were fitted with just 3 these Vaults.[1] The bicurve, lathe-cut lens nstruction, with spherical front and back rfaces, promotes reliable fit independent of wer; and the large posterior optical zone es stability of vision with lens movement.

Additional Advantages

Other significant attributes of the Aquaflex® (tetrafilcon A) lens, contributing to practitioner success and patient acceptance, are: reliable over-refraction,[2,4] ease in handling, durability, excellent reproducibility[2] and exceptionally high standards of quality assurance, including 100% wet inspection. A study has shown that less than 5% of lenses shipped were returned because of questionable performance, discomfort, damage or defects.[1] The fitting procedure is simple and fast.[4] You can fit from a small diagnostic set, or use a dispensing inventory. Lenses may be ordered by a toll-free phone call, and UCO Optics' service is quick and dependable. More and more practitioners are using Aquaflex lenses every day. Shouldn't you?

Aquaflex®
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Hydrophilic Contact Lens

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See following page for full prescribing information.

Data on file: UCO Optics, Inc., Scottsville, N.Y. 14546
Morrison, Robert J.: International Contact Lens Clinic, mmer 1976
Gruber, Ellis & Gordon, Stanley: Contact Lens Forum, bruary 1977
Greenspoon, Morton K.: Contact Lens Forum, vember 1977.

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Aquaflex®
(tetrafilcon A)
Hydrophilic Contact Lens

DESCRIPTION

AQUAFLEX® (tetrafilcon A) Hydrophilic Contact Lens is a hemispherical shell which covers the cornea and may cover a portion of the adjacent sclera. The lens material, tetrafilcon A, is a hydrophilic random terpolymer of 2-hydroxyethyl-methacrylate, N-vinyl-2-pyrrolidone and methylmethacrylate. The polymer is a three-dimensional network of terpolymer chains joined by divinylbenzene cross-links. It consists of 57.5% tetrafilcon A and 42.5% water by weight when fully hydrated in normal saline solution. Lenses have a nominal diameter of 13 mm.

ACTIONS

In its hydrated state the AQUAFLEX® Hydrophilic Contact Lens is soft and pliable. When dry, the lens becomes hard and brittle. These states are completely reversible and a lens which has been permitted to dry out will recover all of its hydrated properties when placed in normal saline for a period of two hours. When placed on the human cornea the hydrated lens acts as a refracting medium to compensate spherical ametropias. The material has a refractive index of 1.43 and the lens has a visible light transmittance greater than 97%.

INDICATIONS

AQUAFLEX® Hydrophilic Contact Lenses are indicated for the correction of vision in persons with non-diseased eyes who have spherical ametropias, corneal astigmatism of 2.50 diopters or less and/or refractive astigmatism of 2.00 diopters or less.

CONTRAINDICATIONS

AQUAFLEX® Hydrophilic Contact Lenses are contraindicated in the presence of any of the following conditions: (1) Acute and subacute inflammation of the anterior segment of the eye. (2) Any eye disease which affects the cornea or conjunctiva. (3) Insufficiency of lacrimal secretion. (4) Corneal hypoesthesia. (5) Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses.

WARNINGS

Medications and Eye Drops: AQUAFLEX® Lenses must be stored in an appropriate solution when off the eyes, the type of solution being dependent on the system used for disinfection. When the lenses are disinfected with the thermal disinfection system, they may be stored *only* in BOILnSOAK® Solution (sterile buffered isotonic solution containing boric acid, sodium borate, sodium chloride 0.7%, preserved with Thimerosal (Lilly) 0.001% and edetate disodium 0.1%). When lenses are disinfected with the chemical disinfection system, they may be stored *only* in FLEXSOL® Disinfection and Storage Solution (sterile buffered isotonic solution of sodium chloride, sodium borate, boric acid, polyvinylpyrrolidone, polyoxyethylene and polyoxypropylene, preserved with Thimerosal (Lilly) 0.001%, chlorhexidine 0.005% and edetate disodium 0.1%).

No ophthalmic solutions or medications, including hard contact lens solutions, can be used by AQUAFLEX® Lens wearers prior to or while the lenses are in place on the eyes. Also, no solutions, including hard contact lens solutions, other than BOILnSOAK® Solution or FLEXSOL® Solution may be used on AQUAFLEX® Lenses when they are off of the eyes.

Since liquids and vapors may be absorbed by AQUAFLEX® Lenses, they should not be placed in the mouth for wetting, nor wiped with a cloth or tissue.

Abrasions and Infections: If a lens becomes less comfortable than it was when first placed on the wearer's cornea, the lens should be removed immediately and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present, or any abnormal eye condition is observed concurrently with lens wear, the lens should be removed immediately and a physician consulted.

Wearing Restrictions: AQUAFLEX® (tetrafilcon A) Hydrophilic Contact Lenses should not be worn while swimming, sleeping, or in the presence of irritating fumes or vapors.

Visual Blurring: If visual blurring occurs, the lens must be removed until the condition subsides.

Lens Care Regimen: Patients must adhere to the recommended daily care procedures for AQUAFLEX® Hydrophilic Contact Lenses. Failure to follow this procedure may result in the development of serious ocular infections.

PRECAUTIONS

Storage: AQUAFLEX® Lenses may be stored *only* in the appropriate storage solution: BOILnSOAK® Solution or FLEXSOL® Solution depending on disinfecting methods used. If left exposed to air, the lenses will dehydrate, become brittle and break readily. If a lens dehydrates, it should be soaked in either BOILnSOAK® Solution or FLEXSOL® Solution until it returns to a soft, supple state.

Cleaning and Disinfecting: AQUAFLEX® Lenses *must* be both cleaned and disinfected daily. Separate procedures and products are needed to clean and to disinfect. Two methods of disinfection, thermal or chemical, have been shown to be equally effective. The choice of disinfection system should be made in consultation with your eye care practitioner.

Cleaning: Daily cleaning is necessary to remove mucus and other deposits which may have accumulated on the lens surface. Each time the lenses are removed from the wearer's eyes, both surfaces of the lenses must be cleaned using several drops of PREFLEX® Cleaning Solution (sterile buffered isotonic aqueous solution consisting of sodium phosphates, sodium chloride, tyloxapol, hydroxyethylcellulose and polyvinyl alcohol with Thimerosal (Lilly) 0.004% and edetate disodium 0.2% added as preservatives). Lenses must be cleaned before they are disinfected, as deposits on the lenses tend to harden and become more difficult to remove after the lenses are disinfected.

Disinfecting: AQUAFLEX® Lenses may be disinfected with either a heat or chemical regimen. One method or the other must be selected, but not both. The user must not alternate between methods.

Thermal Disinfection Method: AQUAFLEX® Lenses may be effectively disinfected after cleaning with PREFLEX® Cleaning Solution with use of the AQUASEPT® Patient Unit and BOILnSOAK® Solution. Fresh BOILnSOAK® Solution must be used for daily storage of lenses or each time the lens is stored. The AQUASEPT® Patient Unit requires distilled water. The AQUAFLEX® Lens Storage Containers must be emptied and filled with fresh BOILnSOAK® Solution just prior to disinfecting the lenses.

Chemical Disinfection: Disinfection with PREFLEX® Cleaning Solution, FLEXSOL® Solution and NORMOL® Rinsing Solution (sterile buffered isotonic aqueous solution of sodium chloride, sodium borate and boric acid, preserved with Thimerosal (Lilly) 0.001%, edetate disodium 0.1% and chlorhexidine 0.005%) has also been shown to be an effective disinfection system for daily care of AQUAFLEX® Lenses. AQUAFLEX® Lenses must be cleaned and rinsed daily (or after wearing) with PREFLEX® Cleaning Solution and NORMOL® Rinsing Solution. The AQUAFLEX® Lens Storage Containers must be emptied and refilled with fresh FLEXSOL® Solution each time the lens is stored. Fresh FLEXSOL® Solution must be used daily for storage and disinfection. WARNING: DO NOT MIX OR ALTERNATE THE DISINFECTION AND STORAGE SYSTEMS. FLEXSOL® SOLUTION SHOULD NOT BE USED WITH HEAT.

Hygiene: Before handling the lenses, hands must be washed, rinsed thoroughly and dried with a lint-free towel. Cosmetics, lotions, soaps, oils and hand creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the spray has settled.

Fluorescein: Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with normal saline solution and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein.

ADVERSE REACTIONS

Serious corneal damage may result from wearing lenses which may have soaked in hard contact lens solutions. Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation.

Very rarely a lens may adhere to an eye as a result of a patient sleeping with the lens on, or as a result of wearing a hypotonic lens. If a lens adheres for any reason, the patient may be instructed to apply a few drops of BOILnSOAK® Solution (if using a thermal disinfection regimen) or ADAPETTES® Lubricating Solution (buffered isotonic aqueous solution containing ADSORBOBASE® [polyvinylpyrrolidone with other water soluble polymers] with Thimerosal (Lilly) 0.004% and edetate disodium 0.1% added as preservatives) (If using a chemical disinfection regimen), and wait until the lens moves freely before removing it.

Clinical studies indicate that corneal edema as manifested by symptoms such as rainbows or halos around light or visual blurring may occur if lenses are worn continuously for too long a time. Removal of the lenses and a rest period of at least one hour generally relieve these symptoms. If symptoms do not subside promptly, professional consultation should be obtained.

Excessive tearing, unusual eye secretions and photophobia are not normal; if these symptoms occur, the patient should be examined to determine their cause.

DOSAGE AND ADMINISTRATION

Fitting: Conventional methods of fitting contact lenses do not apply to AQUAFLEX® (tetrafilcon A) Hydrophilic Contact Lenses. For a detailed description of the fitting technique, refer to the Professional Fitting Guide for AQUAFLEX® Hydrophilic Contact Lenses, copies of which are available from: UCO Optics, Inc., Scottsville, New York 14546.

Wearing Schedule: There may be a tendency for the patient to overwear the lenses initially. Therefore, the importance of adhering to the following initial daily wearing schedule should be stressed to the patient.

Day	Wear Time (*Hours*)	Rest Period (*Hours*)	Wear Time (*Hours*)
1	4	2	4
2	4	2	4
3	5	2	5
4	6	2	5
5	7	2	5
6	7	1	6
7	8	1	7
8	8	1	8
9	9	1	8
10-14	10	1	balance of
15	all waking hours		waking hours†

†lenses should never be worn 24 hours a day

Lens Care and Handling: Care must be taken on the initial visit to assure that the patient is supplied with an appropriate AQUAFLEX® Patient Care Kit and fully understands all care and handling instructions for the lenses. As with any contact lens, regular recall visits are necessary to assure patient health and compliance with instructions.

How Supplied: Each lens is supplied sterile in a glass vial containing normal saline solution. The glass vial is marked with the vault number, dioptric power, and manufacturing identification number.

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BOILnSOAK® Solution	Catalog No. A1301
AQUAFLEX® Patient Instruction Book	Catalog No. X0102

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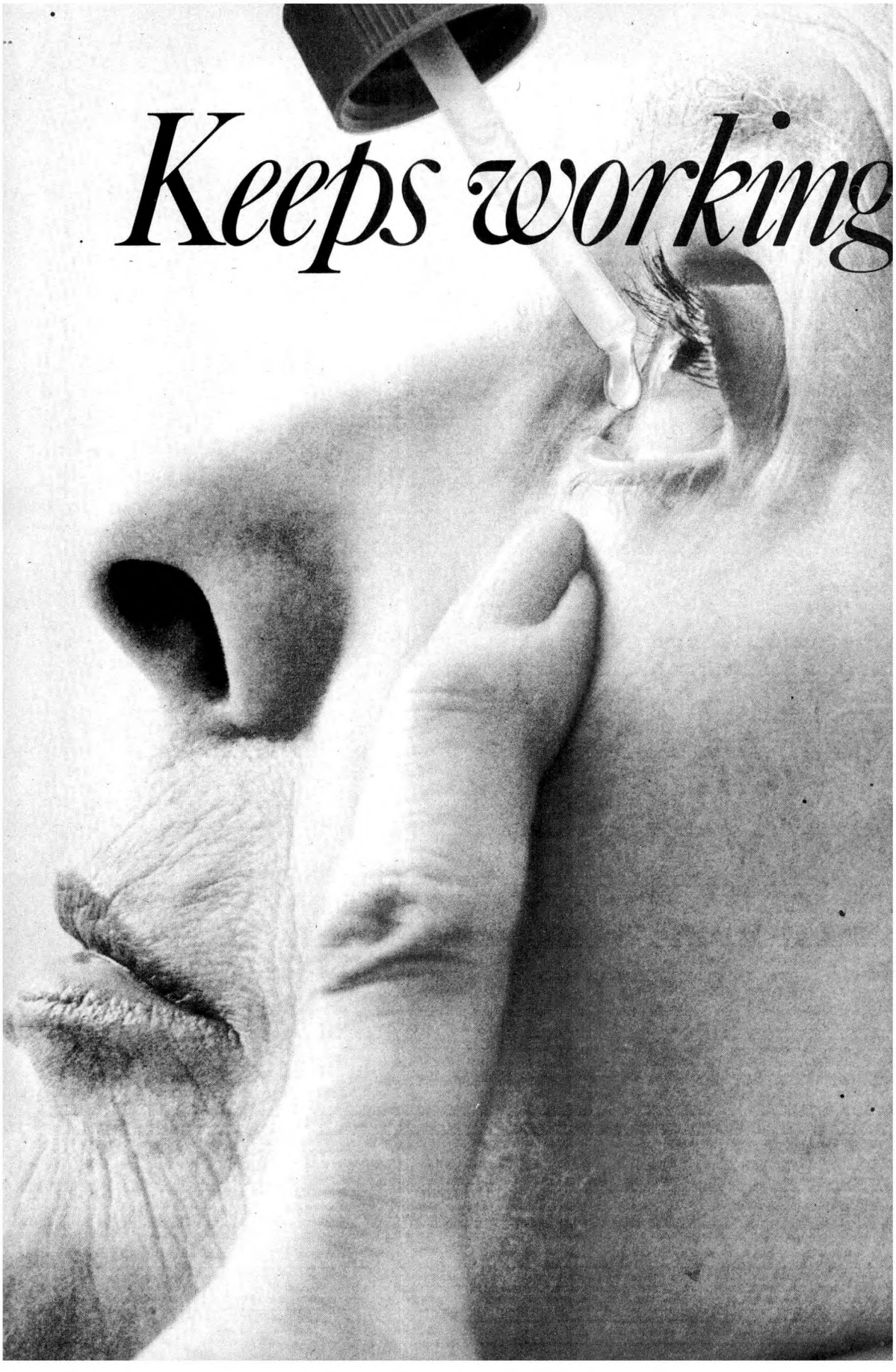
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2. Most cases of angle-closure glaucoma, due to the possibility of increasing angle block.

3. Hypersensitivity to the active or inactive ingredients.

Warnings: 1. *Use in Pregnancy:* Safe use of anticholinesterase medications during pregnancy has not been established, nor has the absence of adverse effects on the fetus or on the respiration of the neonate.

2. Succinylcholine should be administered only with great caution, if at all, prior to or during general anesthesia to patients receiving anticholinesterase medication because of possible respiratory or cardiovascular collapse.

3. Caution should be observed in treating glaucoma with PHOSPHOLINE IODIDE in patients who are at the same time undergoing treatment with systemic anticholinesterase medications for myasthenia gravis, because of possible adverse additive effects.

Precautions: 1. Gonioscopy is recommended prior to initiation of therapy.

2. Where there is a quiescent uveitis or a history of this condition, anticholinesterase therapy should be avoided or used cautiously because of the intense and persistent miosis and ciliary muscle contraction that may occur.

3. While systemic effects are infrequent, proper use of the drug requires digital compression of the nasolacrimal ducts for a minute or two following instillation to minimize drainage into the nasal chamber with its extensive absorption area. The hands should be washed immediately following instillation.

4. Temporary discontinuance of medication is necessary if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, or cardiac irregularities occur.

5. Patients receiving PHOSPHOLINE IODIDE who are exposed to carbamate or organophosphate type insecticides and pesticides (professional gardeners, farmers, workers in plants manufacturing or formulating such products, etc.) should be warned of the additive systemic effects possible from absorption of the pesticide through the respiratory tract or skin. During periods of exposure to such pesticides, the wearing of respiratory masks, and frequent washing and clothing changes may be advisable.

6. Anticholinesterase drugs should be used with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects.

7. Anticholinesterase drugs should be employed prior to ophthalmic surgery only as a considered risk because of the possible occurrence of hyphema.

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Adverse Reactions: 1. Although the relationship, if any, of retinal detachment to the administration of PHOSPHOLINE IODIDE has not been established, retinal detachment has been reported in a few cases during the use of PHOSPHOLINE IODIDE in adult patients without a previous history of this disorder.

2. Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, browache, induced myopia with visual blurring may occur.

3. Activation of latent iritis or uveitis may occur.

4. Iris cysts may form, and if treatment is continued, may enlarge and obscure vision. This occurrence is more frequent in children. The cysts usually shrink upon discontinuance of the medication, reduction in strength of the drops or frequency of instillation. Rarely, they may rupture or break free into the aqueous. Regular examinations are advisable when the drug is being prescribed for the treatment of accommodative esotropia.

5. Prolonged use may cause conjunctival thickening, obstruction of nasolacrimal canals.

6. Lens opacities occurring in patients under treatment for glaucoma with PHOSPHOLINE IODIDE have been reported and similar changes have been produced experimentally in normal monkeys. Routine examinations should accompany clinical use of the drug.

7. Paradoxical increase in intraocular pressure may follow anticholinesterase instillation. This may be alleviated by prescribing a sympathomimetic mydriatic such as phenylephrine.

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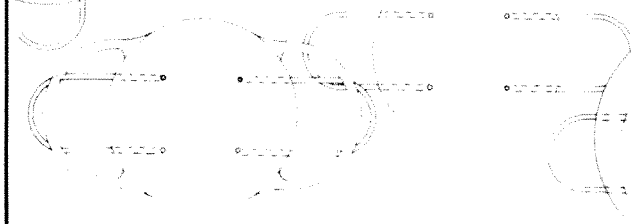
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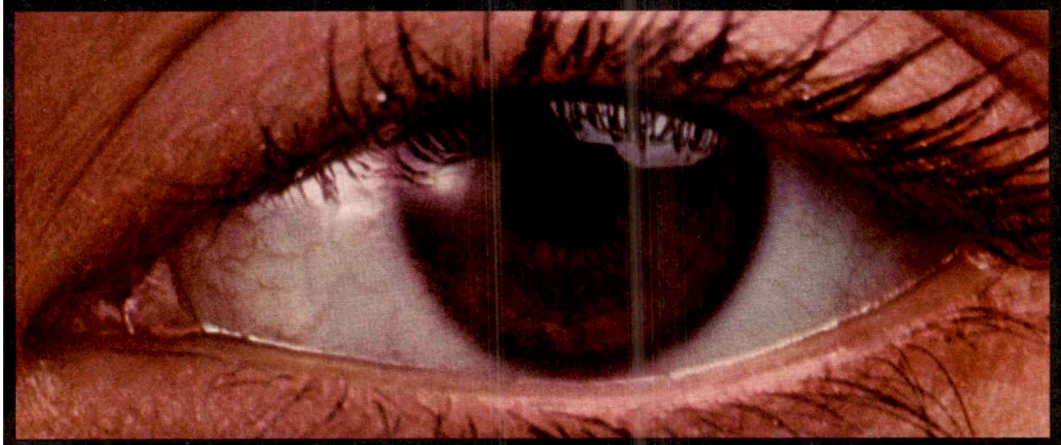
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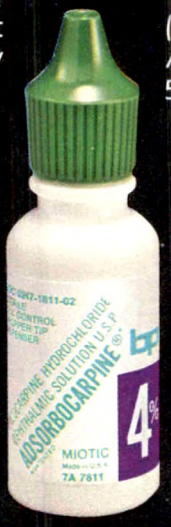
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1. Sherman, Spencer E.: Clinical Comparison of Pilocarpine Preparations in Heavily Pigmented Eyes: An Evaluation of the Influence of Polymer Vehicles on Corneal Penetration, Drug Availability and Duration of Hypotensive Activity, Ann. Ophthalmol. 9:1331, Oct. 1977.


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SOME RATIONALIZATIONS ON CHRONIC OPEN-ANGLE GLAUCOMA

ALBERT M. POTTS, M.D.

Louisville, Kentucky

Sanford Gifford was the super clinician of his time. His quick mind and his broad background made him stand out among his associates and gave him the complete respect of his residents.

His 160 publications including two books covered every major subject in clinical ophthalmology from cataract to plastic surgery, from strabismus to corneal ulcer. Therefore, it is not all surprising that two Gifford publications concern glaucoma.[1,2]

The following is particularly appropriate 42 years after it was written[2]:

> It must be repeated that most cases of glaucoma and especially of primary glaucoma, will, sooner or later, require surgical intervention. Most of us have seen more harm done in cases of glaucoma by delaying surgery than by operations improperly performed. This is due chiefly to late diagnosis, failure to use the tonometer and perimeter as a routine where any suspicion of glaucoma arises. It is also due, unfortunately, to the fact that many well-trained ophthalmologists do not have enough confidence in their operative skill or experience to insist upon surgery when the proper time for it arrives. The fear of possible operative failure should never lead one to persist in non-surgical treatment when records of fields and tension show that the condition is not under control.

We know now that the increased breadth of our medical capabilities allows some patients to live a comfortable life without loss of vision and without surgery. However, the idea that no patient will ever need glaucoma surgery, which was so prominent in the last 20 years, is equally erroneous.

A significant portion of the Gifford paper[2] is devoted to the use of epinephrine as a therapeutic agent for glaucoma, complete with proper caution about the mydriatic effect of epinephrine if used alone. As with the use of surgery, the use of epinephrine has had to be neglected, then rediscovered in the intervening 45 years.

These facts are irrational enough but they are not what has struck me most in my dealings with glaucoma over the years. (The irrationalities are only seemingly irrational of course, nature knows what she is doing, it is we who are too dense to grasp what is going on.) Of all the puzzles glaucoma presents, let me submit two for your special consideration: (1) How does the small percentage increase of intraocular pressure in chronic open-angle glaucoma operate to cause the specific symptoms of that disease? (2) How may we go about improving glaucoma surgery to make it an equal partner with medical treatment?

To deal with the most tractable of these ideas, let us deal with the second subject first.

Surgery for chronic open-angle glau-

From the Department of Ophthalmology, University of Louisville School of Medicine, Louisville, Kentucky. This study was supported in part by the United States Public Health Service Research Grant Number EY 01941 from the National Eye Institute, National Institutes of Health, Bethesda, Maryland, and by the L. L. Sinton Trust Research Grant. Presented as the 33rd Annual Gifford Memorial Lecture before the 29th Annual Clinical Conference of the Chicago Ophthalmological Society, May 20, 1977.

Reprint requests to Albert M. Potts, M.D., Department of Ophthalmology, University of Louisville School of Medicine, 301 E. Walnut St., Louisville, KY 40202.

coma—Perhaps the most important concept in glaucoma surgery is that there is no single best operation for glaucoma. There are a number of procedures each with its own specific virtues and its individual drawbacks. A good glaucoma surgeon should have a series of such operations at his command and suit the procedure to the needs of the patient.

The gentlest of such procedures is cyclocryotherapy. It seems to have given us a new and important instrumentality. Controlled destruction of the aqueous-forming ciliary processes is not a new idea. In the late 1940s Berens, Sheppard, and Duel[3] introduced cycloelectrolysis, and cyclodiathermy is as old as the 1956 publication of Vogt.[4] However, in terms of predictability of results, cyclocryotherapy seems to have advantages not obtained with other destructive methods. Although the concept was introduced by Bietti[5] as early as 1947, adoption had to await the advent of equipment that could freeze under repeatable and controlled conditions. The first such equipment was the Union Carbide cryosurgical unit originally devised for cataract extraction and used by Kelman.[6] This equipment was adapted for cyclocryotherapy by deRoetth.[7] There are a number of advantages not shared by other techniques:

1. The neglible effect on sclera and conjunctiva as compared to other modalities is important.

2. The efficacy when only 180 degrees of ciliary body is treated gives a comfortable margin of safety against phthisis bulbi.

3. Repetition once or even twice is feasible.

4. The technique appears to be particularly effective in eyes which have neglected open-angle glaucoma with small remaining central fields.

We get modest pressure reductions with this technique, so it is useful in the cases where intraocular pressures (IOP) are in the mid to low 20s and we need them in the mid-teens. A common observation is that after severe optic nerve damage, an IOP of 20 mm Hg cannot be sustained without further damage, hence the usefulness of such a relatively mild procedure.

It may be that the old legend about the hazard of extinguishing a small central field by a filtering operation arose from rare cases of central serous choroidopathy which can happen whenever the IOP goes to zero as in a filter or a cataract procedure. Cyclocryotherapy never drops the IOP to zero and one would not expect central serous choroidopathy to result.

SURGERY FOR MAXIMUM EFFECT—For significant pressure reduction of 20 mm Hg or so, for example, a reduction from 38 to 18 mm Hg, we must do a filtration procedure. The first axiom we must establish is that the essence of such surgery is to create new, nonphysiologic, pathways for the departure of aqueous humor from the eye to substitute for the incompetent natural pathway. This implies the following:

Simple iridectomy is not therapeutic in open-angle glaucoma. There may well be temporary reduction in IOP after any intraocular procedure. There is nothing about iridectomy that will allow increased outflow unless it is inadvertent cyclodialysis.

We still rely mainly on classical filtering procedures. Included among these are: (1) corneoscleral trephine; (2) LaGrange sclerectomy and its modifications as in thermal sclerostomy; and (3) trabeculectomy, which one has to consider as a filtering procedure until proven otherwise.

The classic filtration procedure, the Elliot trephine,[8] has many advantages. In particular, the size of the aperture created is kept constant by the use of a trephine.

A second advantage is that for any given cross-section area a filtering aperture with circular shape is one least likely to be obstructed. The threat that haunts all filtering operations is eventual scarring shut and cessation of filtration. The circular aperture avoids any geometric contribution to closure.

A distinct disadvantage of the trephine operation is that force is applied to a sharp instrument directed at the lens. Even though the button may not be severed cleanly (but this frequently happens), the instrument or the hinged button may contact the lens as the anterior chamber collapses. Because of this serious disadvantage, many surgeons have abandoned trephining in favor of operations that avoid this potential problem.

I personally prefer a variant of the LaGrange anterior lip sclerectomy as follows:

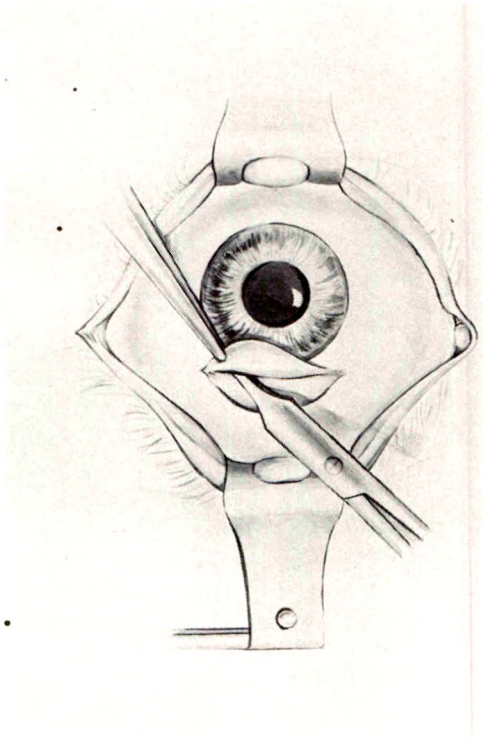


Fig. 1 (Potts). Anterior lip sclerectomy. Creation of limbal-based flap.

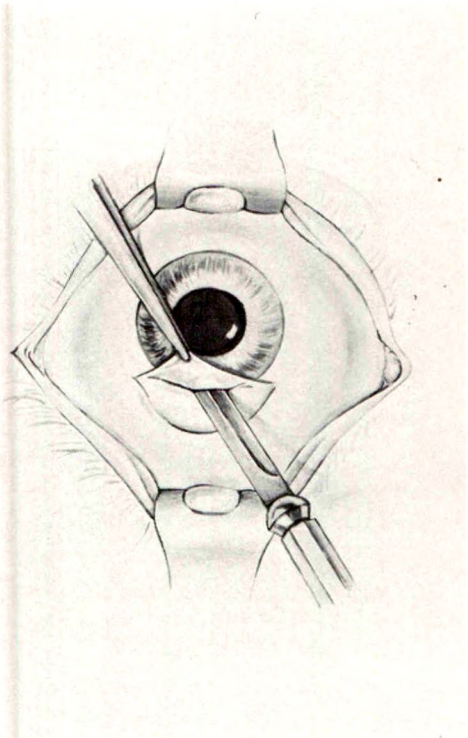


Fig. 2 (Potts). Anterior lip sclerectomy. Corneoscleral splitting.

A superior rectus stay suture is placed and stabilized.

A limbal-based conjunctival flap centered at 12 o'clock is created (Fig. 1).

Corneoscleral splitting is done with a No. 64 Beaver knife (Fig. 2).

Linear incision is done with a No. 67 Beaver knife 1.5 mm posterior to the corneoscleral limbus (Fig. 3). Because the anterior lip is elevated with forceps after the first cut, the underlying structures are not penetrated.

While the anterior lip is elevated, a piece of corneoscleral junction is excised with curved scissors (Fig. 4). Once again because of the elevation, there is no possibility of contacting the lens with an instrument.

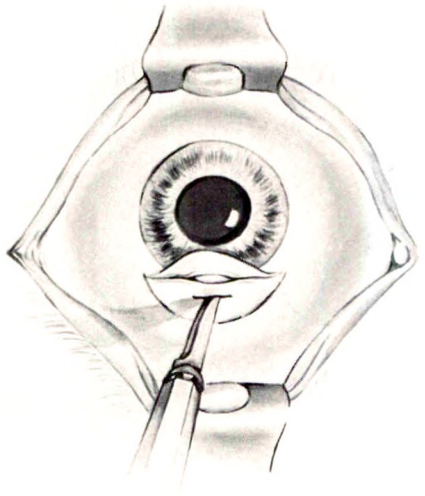


Fig. 3 (Potts). Anterior lip sclerectomy. Scleral incision.

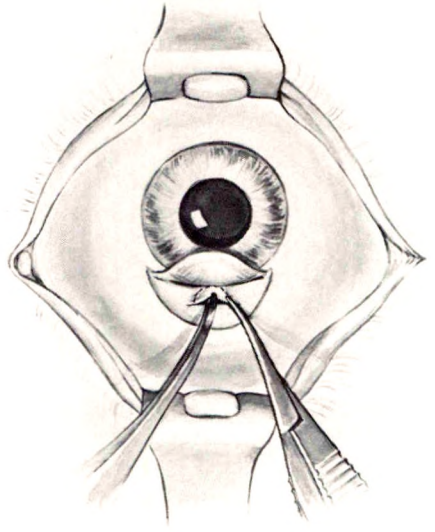


Fig. 4 (Potts). Anterior lip sclerectomy. Excision of anterior lip.

In an operation of this type, control of the size of the opening is important. To obtain a sclerectomy opening of the same area as the 2-mm diameter circular trephine opening, which is satisfactory in the Elliot operation, the following must be considered:

The area of a 2-mm diameter circle is 3.14 mm^2 (Fig. 5).

To excise a semicircle of the same area requires a diameter of 2.83 mm (Fig. 6).

If the area excised is flatter, such as a segment of one-third the total area of a circle, the base must be even larger, almost 4 mm (Fig. 7). These shapes drawn to scale are graphically different (Fig. 8).

Because of sharp corners these noncircular shapes are likely to close faster. Therefore, all other things being equal, the noncircular shapes should have more area then the equivalent circle.

My equalizer is to cauterize the posterior lip.

Following the excision, an iridectomy is performed (Fig. 9), the sclera is cauterized, and the conjunctival flap is closed with a running absorbable suture (Fig. 10).

PREZIOSI PROCEDURE AS MODIFIED BY SCHEIE—The principle of the Preziosi procedure[9] as modified by Scheie[10] was thought by Scheie to be based on retraction of the wound edge caused by thermal shrinkage of scleral collagen. Regan[11]

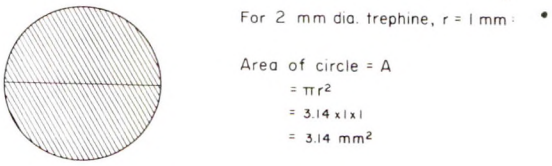


Fig. 5 (Potts). Area of trephine 2 mm in diameter.

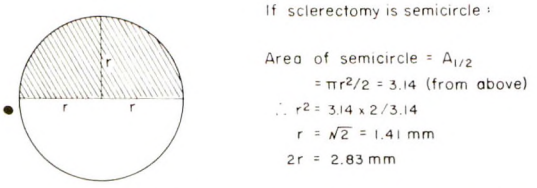


Fig. 6 (Potts). Sclerectomy of semicircle equal to trephine 2 mm in diameter.

demonstrated that in experimental animals coagulation of the sclera inhibited postoperative scarring by a mechanism that is still unknown.

Thus, I prefer to add thermal coagulation to the posterior lip of the sclerectomy incision as a part of my routine maximum surgical procedure.

In all of the variants of the maximal procedure certain sequellae are expected, the chief of these being a flat anterior chamber that persists for one to five days. The absence of a flat chamber leads one to suspect some flaw in the execution of the procedure. This expected occurrence favors the formation of peripheral anterior synechiae. Conceivably, lens-cornea contact during the flat chamber period accelerates cataractogenesis. Where such a maximal procedure is required one has no choice but to endure these undesirable side effects, combatting them with anti-inflammatory drugs and moving the pupil with local medication where these procedures are appropriate.

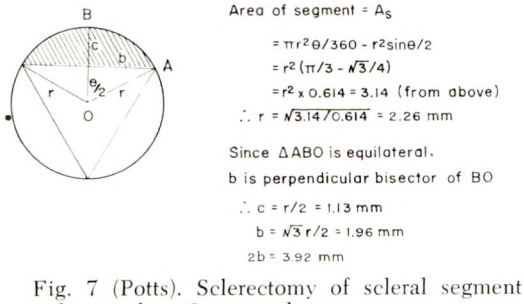


Fig. 7 (Potts). Sclerectomy of scleral segment equal to trephine 2 mm in diameter.

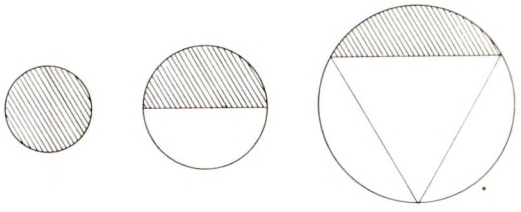


Fig. 8 (Potts). Sclerectomy of area equal to trephine 2 mm in diameter.

The intermediate procedures—TRABECULECTOMY—Recently a new category of procedures has been under exploration based on the trabeculectomy of Cairns.[12,13] The original idea that in trabeculectomy a section of Schlemm's canal is excised to allow aqueous outflow through the cut ends (bypassing incompetent trabecular meshwork) is probably incorrect. Nevertheless, the procedure as outlined by Cairns[13] does reduce IOP for

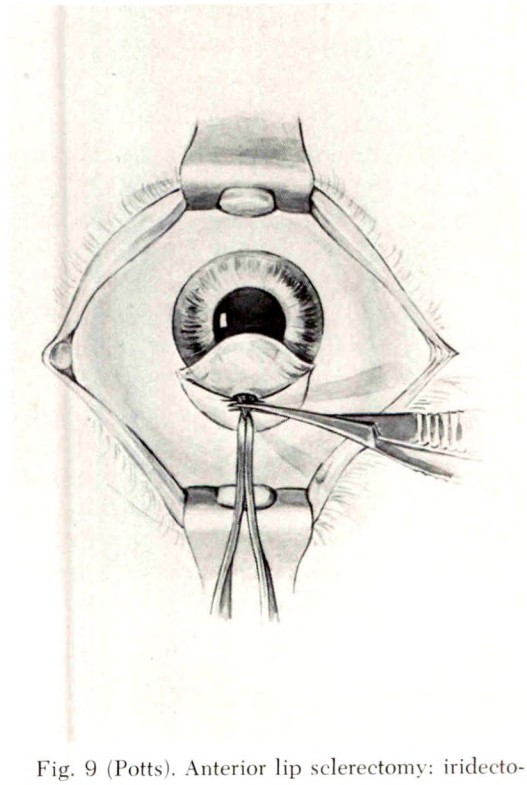


Fig. 9 (Potts). Anterior lip sclerectomy: iridectomy.

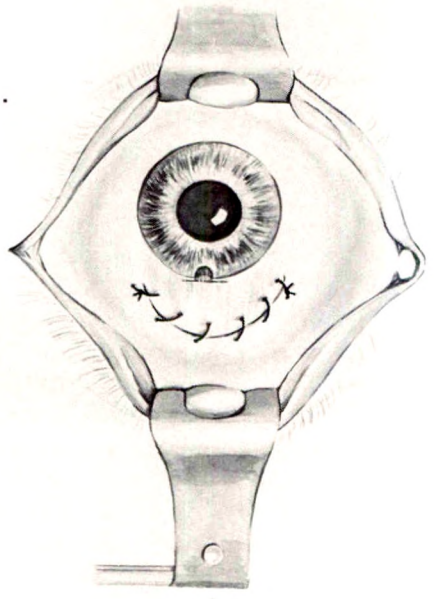


Fig. 10 (Potts). Anterior lip sclerectomy: closure.

extended periods of time and it has the advantage of not causing a flat anterior chamber for many days. It requires a modicum of skill and the use of the operating microscope, which is routine for the modern opthalmic surgeon.

In my experience the pressure-lowering effect is somewhat less than that obtained by sclerectomy (or a 2-mm trephination) and the procedure should not be used where maximum pressure lowering is required. It may well return an eye with pressure in the low 30s to the normal range for an extended period of time.

I find that trabeculectomy is an unsatisfactory operation for young people and for blacks. It appears to be more susceptible to scarring shut than the classic filtering procedure.

The procedure I favor varies from that of Cairns. After reflection of a limbal-based flap of conjunctiva, a half-thickness scleral flap is outlined on three sides and hinged at the corneoscleral limbus. The scleral flap is centered at 12 o'clock and is 5 mm wide by 4 mm long. It is outlined by a guarded razor blade set to 0.5 mm depth[14] (Fig. 11). The scleral flap is undermined with the No. 66 Beaver blade and the corneal hinge is extended by splitting past the scleral spur (Fig. 12). This is determined by using a fiber optic light pipe.

The scleral flap is reflected and the remaining sclera is incised to the ciliary body at a point 3 mm posterior to the base of the hinge. A special short cyclodialysis spatula is inserted in the incision and a cyclodialysis is performed (Fig. 13). A 3 × 3-mm square of sclera including the scleral spur is excised with a straight-bladed angulated spring scissors (Fig. 14). A basal iridectomy is then performed

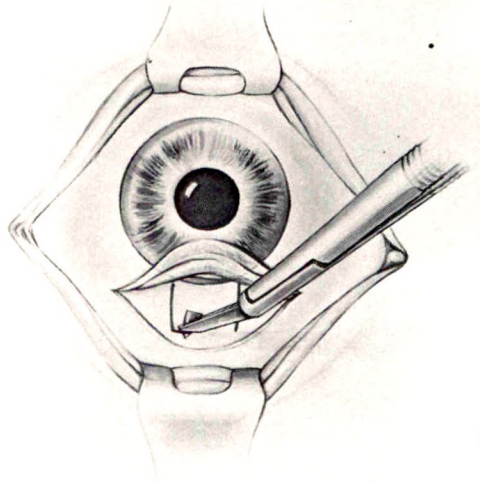


Fig. 11 (Potts). Trabeculectomy: half thickness incision.

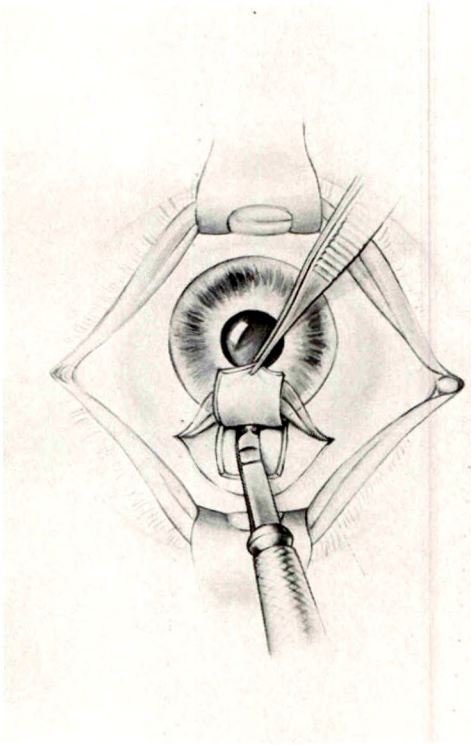


Fig. 12 (Potts). Trabeculectomy: reflection of scleral flap.

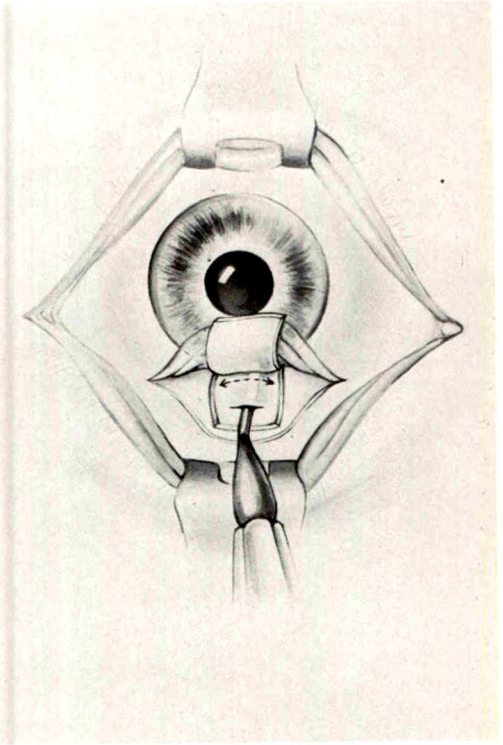


Fig. 13 (Potts). Trabeculectomy: cyclodialysis.

(Fig. 15). The scleral flap is resutured with 7-0 or 8-0 synthetic absorbable suture material. Generally, each corner is sutured and a suture is placed in the middle of each edge (Fig. 16). The conjunctival flap is closed with a running suture of 7-0 synthetic absorbable material.

The rationale for this technique is based on the analysis of Spencer.[15] The four possibilities he described seem to exhaust the logical possibilities for mechanism of action, but whether one or each of the four is operative in the relief of IOP is uncertain.

The least likely possibility is the original rationale presented for trabeculectomy; namely, that the route of outflow is into Schlemm's canal via the cut edges of the scleral spur.

Outflow may be via the limbal scleral vessels whose ends have been severed by the lamellar sclerectomy, thus creating a series of perforating channels. Alternatively, flow may be through the entire thinned scleral flap. In either case, the larger the excised portion of the sclera, the more effective the procedure. This is the reason for the excision of a 3-mm square.

One may be creating a filter that leaks around the margin of the scleral flap. If this mechanism is the predominant one, the larger the perimeter of the flap, the better the filtration should be. The flap should not be held in place with a large number of sutures. This is the reason for a large square flap rather than a small triangular one.

One may be getting outflow through the retrociliary space as in a standard cyclodialysis via whatever uveoscleral path-

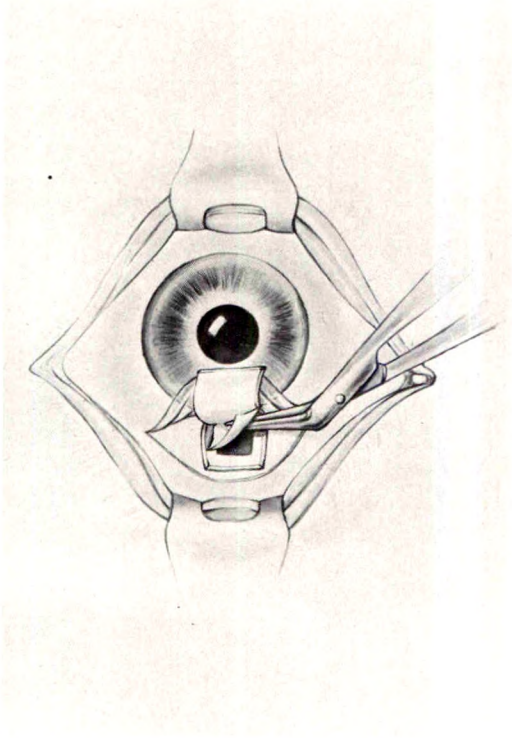


Fig. 14 (Potts). Trabeculectomy: scleral excision.

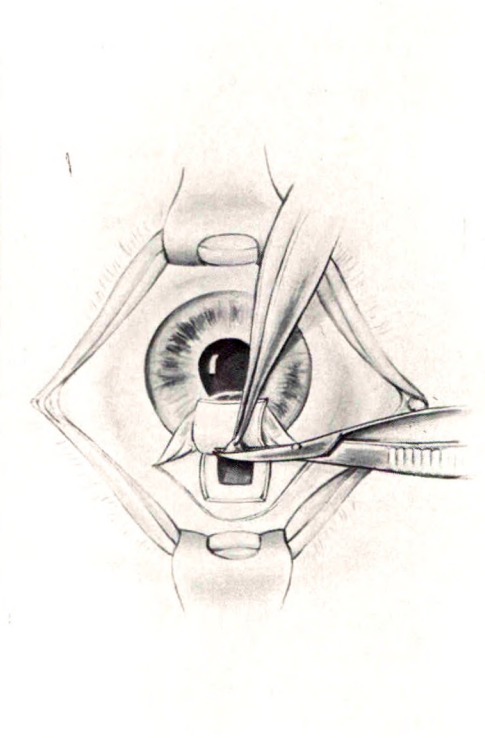


Fig. 15 (Potts). Trabeculectomy: iridectomy.

ways exist.[16] For this reason, cyclodialysis assures maximal drainage by that route.

Special situations in glaucoma surgery—SURGERY IN NEOVASCULAR GLAUCOMA—The stumbling block in surgery for neovascular glaucoma has been the disastrous intractable hemorrhage that results when the new vessels are severed by iridectomy.

A recent report describes treatment of neovascular glaucoma by photocoagulating the new vessels in the chamber angle.[17] A procedure we began to use three years ago is based on a somewhat different principle (unpublished data). Using a Goldmann goniolens and an argon laser, we photocoagulate the root of the iris in the 12 o'clock position only. The new vessels in the iris stroma are destroyed by closely placed laser burns. Since the main feeder vessels from the greater arterial circle in the normal iris are radial, these too are occluded. Thus the blood supply to the iris, normal and neovascular, is interrupted for approximately 1½ clock hours centered at 12 o'clock. When an anterior sclerectomy is performed, it can be completed without complication because the iridectomy is bloodless. This procedure has proved successful in four siblings with hereditary juvenile glaucoma with vascularization of the chamber angle, in one case of Pierre Robin syndrome with vascularization of the angle, and with five cases of diabetic neovascular glaucoma. This approach is an alternative treatment for neovascular glaucoma.

EXPERIMENTAL GLAUCOMA SURGERY—If we are to rely upon filtering procedures for one and possibly two of the operations in our antiglaucoma repertoire (sclerectomy and trabeculectomy), our

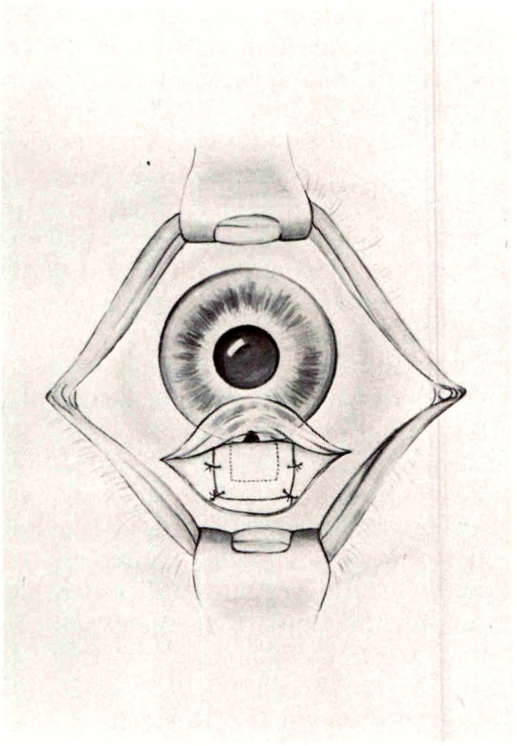


Fig. 16 (Potts). Trabeculectomy: closure.

objective is to assure successful filtration. Tradition has it (and nothing in my experience contradicts this) that a filtering procedure fails when the fistula between the anterior chamber and the subconjunctival space scars shut and no longer passes aqueous. In the past, attempts to prolong filtration chiefly centered around insertion of setons.[18] These procedures have not had notable success.

Recent work in our laboratory has been directed toward modifying the nature of the scar so that its chemical composition is altered. Our study is based on the finding that a diet containing a particular type of bean causes skeletal deformation in man and experimental animals. Because the beans in question are of the genus *Lathyrus* the condition is known as "lathyrism." Later research has shown that the actual toxic substances are aliphatic short chain nitriles the most effective of which is β-amino propionitrile. The "lathyrogen" causes an abnormal collagen to be laid down. The collagen is deficient in cross linkages and is much more soluble in salt solutions than is normal collagen. Thus, if one could cause local lathyrism in the area of a filtering procedure for glaucoma, the lathyritic collagen would be more highly permeable to aqueous and would continue to be so over a longer period of time than one finds in a standard operation.

Our experiments to create local lathyrism are at their earliest stages but we have implanted a device (Fig. 17) under the conjunctiva of the rabbit in the place of the 5 × 5-mm scleral flap of a trabeculectomy.

The aminoacetonitrile maleate liberated from the agar core and diffusing through the 0.3-μ apertures of the polycarbonate membrane should cause the local lathryism we described. Because

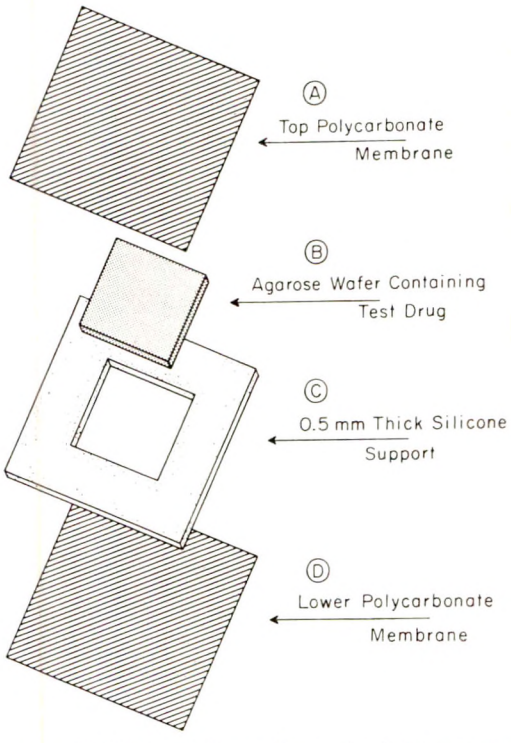


Fig. 17 (Potts). Delivery device for lathyrogen in experimental glaucoma surgery.

glaucoma operations in experimental animals scar shut rapidly, we will consider any functional filter obtained a success. The second potential virtue of our procedure is that, as in the trabeculectomy, the fistulizing area closes, which prevents flat anterior chamber.

We are exploring the many permutations of these principles. The totally absorbable insert containing a lathyrogen or a lytic enzyme such as collagenase has another set of desirable properties.

The pathogenesis of glaucoma—When Sanford Gifford wrote about the pathogenesis of glaucoma, he was concerned with the mechanisms at the chamber angle responsible for inadequate drainage and increase of IOP. In subsequent years this aspect of the disease has been studied in detail. The aspect of the mechanism that fascinates me, however, and seems to me to be the great paradox in chronic open-angle glaucoma is that increase in IOP does selective and consistent damage to only a portion of the nerve fibers.

Ernest and I showed with a pressure probe that the entire intraocular compartment up to the lamina cribrosa was a single pressure compartment responding immediately to changes in IOP.[19] However, if this finding were the determining factor in chronic open-angle glaucoma one would expect the central retinal circulation to control tissue damage. There should be no damage until systolic pressure of the central retinal artery is reached. Beyond this point the entire field should black out. This indeed is what happens in ophthalmodynamometry, in acute glaucoma, and in such experiments as those described by Radius and Maumenee.[20]

The paradox of chronic open-angle glaucoma is that systolic pressure of the central retinal artery is never reached and that the damage shows a characteristic configuration. That characteristic configuration is the arcuate (Bjerrum) scotoma.

Experimental methods at our disposal are poorly adapted to diseases that require years to become manifest. Experiments that must run five to ten years are difficult to execute and even more difficult to support financially. In this case, as in others, we are reduced to arguing by analogy.

Other phenomena that cause arcuate scotomata and allow us to propose an analogy include: pits of the optic disk, juxtapapillary chorioretinitis, and tumors of the disk. Findings in these lesions and in chronic open-angle glaucoma are consonant with what we know of the pattern of the retinal nerve fiber layer. Thus, we can even locate the necessary site of the glaucoma lesion at the disk. The one thing we cannot say with certainty is why moderate increase of IOP causes damage at that point only and why higher increases of pressure cause generalized retinal damage.

Indeed, it has recently become fashionable to question whether ischemia, which is the obvious cause of damage in acute glaucoma, plays any role in chronic open-angle glaucoma. I am not able to prove that ischemia is truly the mechanism in the disease. However, I consider it the chief contender, and I propose a number of possibilities as to why this can be true.

First, consider it possible that the elasticity of the globe, its volume change with every pulse, can cause modification of Pascal's law because we are not dealing with a truly closed system.

The volume change in the eye with pulse pressure is easy enough to measure in a semiquantitative manner and anyone who has looked at a tonographic record has seen this change occur. The irregularities in the tonogram are pulsations of the globe that occur with each systole (Fig. 18). Within the limits of accuracy of the tonographic system that volume change can be measured and with optical methods the measurement is capable of extreme precision (Table).

The first question that one might ask is

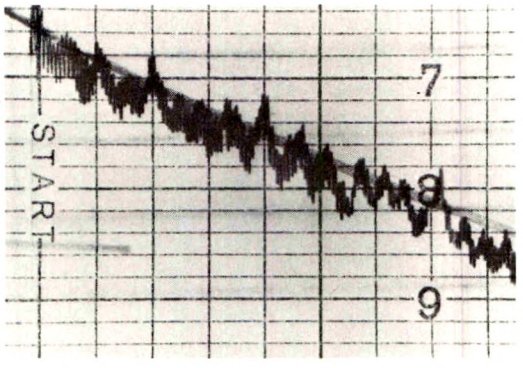


Fig. 18 (Potts). Pulsation of the globe as shown on the tonogram.

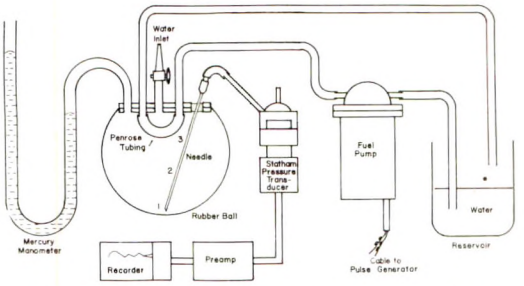


Fig. 19 (Potts). Model using a rubber ball as the eye model and a piece of Penrose drain as the pulsating volume changer.

whether pressure within such a pulsating system is different near the disk where choroidal and retinal volume changes occur as compared to the periphery.

We modeled such a system by using a rubber ball as the eye analog and a piece of Penrose drain as the pulsating volume changer (unpublished data) (Fig. 19). Unfortunately, in our model the pulse pressure was the same close to the pulsation source as it was near the periphery. This was not modified by moderate initial increase of pressure in the ball (= IOP). There are so many postulates implicit in the materials used in this model that its negative result does not eliminate the model. Only if it had given a positive result would the result be definitive.

TABLE

SIGNIFICANCE OF TONOGRAPHY PULSE

Pulse measurement	= 0.5 scale division (6.5-7.0)
1.3/17 mm Hg	= ca 7.6% increase in IOP
Also:	
If volume of eye	= 6500 mm^3
Radius of equivalent sphere	= 11.57 mm
Schiøtz scale:	
20 divisions	= 1 mm
∴0.5 division	= 0.025 mm increase at each heart beat
Equivalent increase in volume	= 29 mm^3 = 0.4%

An additional possibility, which will need the most delicate measurements for its exploration, is as follows:

The intraocular portion of the optic papilla is a separate pressure subcompartment because of its tissue density and because it has a surface membrane.[21] Through it runs the central retinal artery transmitting its pulsations to the subcompartment. However, the nutritional supply to the papilla is a set of capillaries that originate, not from the central retinal artery, but from the choroidal circulation.

The evidence for this comes from a series of injection experiments begun in the 19th century, and which Ernest and I continued.[22]

The central retinal artery goes through the papilla without offering this structure a significant blood supply. The nutrition of the papilla comes partly from choroidal artery branches via the circle of Zinn, and partly from tiny precapillary-sized branches of the short posterior ciliary artery running anterograde in the substance of the optic nerve. The circle of Zinn is supplied by small branches of the short posterior ciliary system that have run intrasclerally. The pressure inevitably drops between the short posterior ciliary artery and the circle of Zinn. A second pressure drop occurs from the

circle of Zinn to the minute capillaries that supply the nerve head. There must be great disparity between the relatively low pressures in these capillaries and the pulsations transmitted to them by the superior and inferior arterioles as they cross the disk. The precise measurement of this pulse pressure is difficult, but extrapolating from the data of Smith,[23] it cannot be greatly different from that in the ophthalmic artery. When measured by ophthalmodynamometry those pulse pressures are consistently found to be between 30 and 40 mm Hg (Fig. 20).[24]

The pressures (and the pulses) in the central retinal vessels and in the choroidal vessels are essentially the same where they enter the eye. At the papilla itself is the strongly pulsating central retinal artery not contributing nutrients and the nutritional capillaries whose pressure barely exceed IOP. At each heartbeat the pressure at the papilla increases, particularly adjacent to the walls of the superior and inferior branches of the central retinal artery. In the presence of these pressure swings, the capillary supply to the papilla is adequate. When the intraocular pressure increases to 28 mm Hg, the change in the central retinal artery is relatively small, but the adjacent capillaries cannot take the change, and somewhere on the way to systole they collapse, causing relative ischemia of the disk.

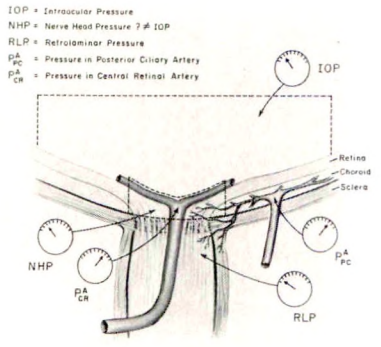


Fig. 20 (Potts). Possible pressure relationships at the optic papilla.

If this pulsation is greatest along the vertically directed superior and inferior arterial branches, it accounts for the reason that the papillomacular bundle is spared and superior and inferior arcuate scotomas are created. It also accounts for vertical extensions of the cup in glaucoma, as described by Kirsch and Anderson.[25] The particular configuration of damage in any eye will be determined by the configuration of the branches of its central vessels.

Summary

In this study I dealt with two principal aspects of the seemingly irrational subject of chronic open-angle glaucoma: surgery for chronic open-angle glaucoma, and the unique pattern of damage encountered in chronic open-angle glaucoma.

Available surgical procedures were treated as a continuous series, depending on the amount of pressure-lowering expected. Vascular interaction was hypothesized to explain the typical pattern of damage.

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COMPARISON OF PARTIAL-THICKNESS AND FULL-THICKNESS FILTRATION PROCEDURES IN OPEN-ANGLE GLAUCOMA

PHILIP H. WATKINS, JR., M.D., AND RICHARD F. BRUBAKER, M.D.

Rochester, Minnesota

The partial-thickness glaucoma filtering procedure, commonly known as trabeculectomy, is a widely used surgical treatment for glaucoma. The theoretic concept of this procedure was introduced by de Vincentiis in 1893,[1] and Barkan[2] coined the term trabeculectomy in the 1930s. However, the surgical procedure currently used was not developed until the 1960s.

Cairns[3] introduced his concept of trabeculectomy in 1968, about the same time that other microsurgical procedures such as sinusotomy and trabeculotomy were being introduced. In 1970, Watson[4] introduced modifications that are now commonly used. Others have added their own modifications and nomenclature, such as the trepanotrabeculectomy,[1] caniculotrabeculectomy,[5] lamellar posterior lip sclerostomy,[5] and thermotrabeculocanalotomy.[6]

Most investigators agree that these microsurgical procedures have advantages over the full-thickness procedures. Some debate remains, however, as to the mechanism whereby these procedures lower intraocular pressure. After a decade, the consensus is that these procedures lower the pressure in the same way as do the full-thickness procedures.[5-12] Therefore, these procedures can be referred to collectively as partial-thickness filtration procedures.

We compared the results of a partial-thickness procedure (trabeculectomy, as described by Watson[4]), with that of a full-thickness procedure (corneoscleral trephination, as described by Sugar[13]), in the management of open-angle glaucoma. All procedures were performed by the same surgeon, and all patients were followed-up for a minimum of one year.

From the Department of Ophthalmology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. This study was supported in part by the National Institutes of Health, Grant EY-00634 of the National Eye Institute.

Reprint requests to R. F. Brubaker, M. D., Section of Publications, Mayo Clinic, Rochester, MN 55901.

SUBJECTS AND METHODS

Patients with medically uncontrolled open-angle glaucoma were used in this study. Those who had angle-closure glaucoma or secondary glaucoma, or who had eyes with previous trauma or surgery of any type, were excluded. All patients were examined by the same physician, and data were collected prospectively. If a filtration procedure was necessary, and either a trephine procedure or a trabeculectomy procedure was chosen, the patient's data were entered into a computer file (Fig. 1).

Patients' eyes were not randomized for the selection of procedure, but those that required the lowest postoperative pressure for control underwent the full-thickness procedure. Postoperative therapy (atropine 1% twice a day for three weeks) was the same in both groups.

The data were analyzed as soon as each group with at least one-year follow-up was large enough for statistical analysis. The Student t-test for population differences and the chi-square test were used for analyzing group differences, with $P<.05$ accepted as significant.

RESULTS

Preoperative evaluation—No statistically significant differences were noted between the two groups in age, sex, race, diagnosis, preoperative medication, or av-

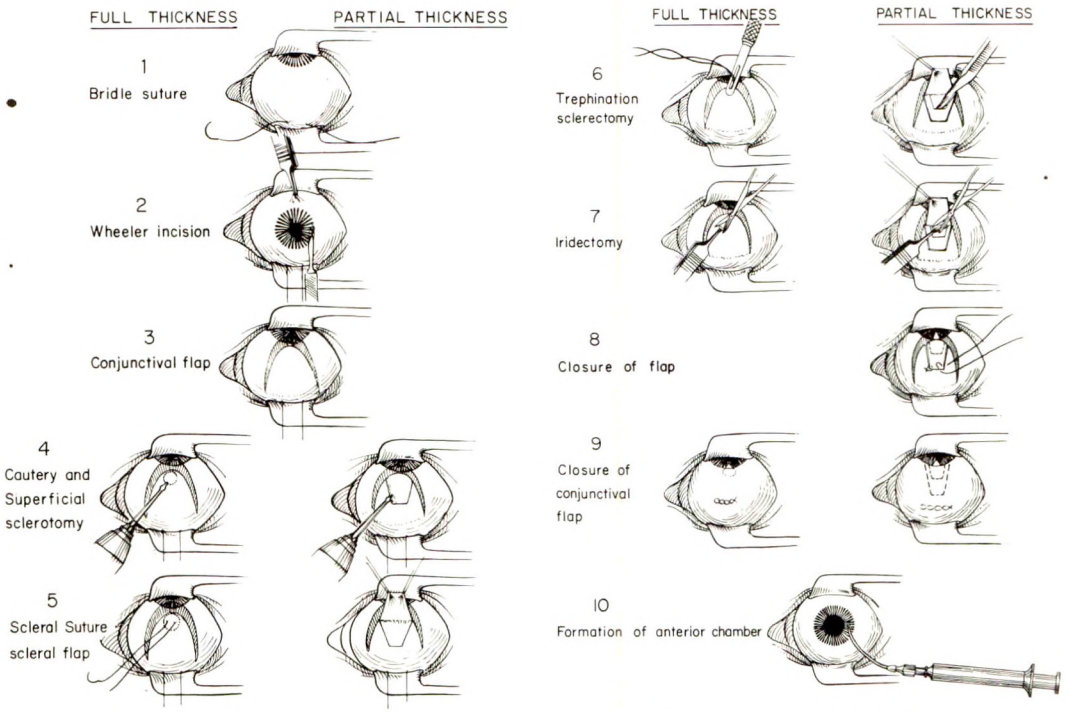


Fig. 1 (Watkins and Brubaker). Surgical steps performed in full-thickness procedure (left) and partial-thickness procedure (right). Steps common to both procedures are shown in the center.

erage preoperative intraocular pressure (Table 1). Statistically significant differences were evident in visual acuity ($P<.001$), cupping of the disk ($P<.025$), and glaucomatous visual field defects ($P<.001$). These differences were expected because the full-thickness procedure was chosen for the eyes that had the most advanced cupping. In the other measured variables, the two groups were comparable before operation.

Immediate postoperative evaluation—In the full-thickness group there was significantly ($P<.001$) greater number of shallow and flat anterior chambers (Table 2). A high incidence of small hyphemas was evident in both groups, but there was no significant difference between the two groups. Intraocular pressures were recorded in only half of the eyes, but the data in the two groups were similar.

Early postoperative evaluation—During the early postoperative period, there was a small but significant ($P<.05$) difference in intraocular pressure, with the full-thickness group having slightly lower pressures (Table 3). Significantly ($P = .005$) fewer filtration blebs were present in the partial-thickness group and there was no significant change in visual acuity in either group. The major postoperative problem was failure of the procedure to control intraocular pressure at a satisfactory level; this was evident in 10% of each group.

Late postoperative evaluation—After a year, the small difference ($P<.05$) in intraocular pressure between the two groups persisted (Table 4). The visual acuity remained unchanged. Approximately 20% of all patients' eyes were receiving one or two medications for glaucoma, but none

TABLE 1

PREOPERATIVE CHARACTERIZATION OF EYES UNDERGOING SURGERY

Patient Data	Total Eyes (No. = 76)	Group: Partial-Thickness Procedure (No. = 49)	Group: Full-Thickness Procedure (No. = 27)
Age at surgery (yrs)			
Median	64	62	65
Range	15-85	15-80	38-85
<65	38	28	10
≧65	38	21	17
Sex			
Male	40 (53%)	26 (53%)	14 (52%)
Female	36 (47%)	23 (47%)	13 (48%)
Race			
White	73 (96%)	47 (96%)	26 (96%)
Black	3 (4%)	2 (4%)	1 (4%)
Open-angle glaucoma	76 (100%)	49 (100%)	27 (100%)
Chronic simple	60 (78%)	36 (74%)	24 (89%)
Pigmentary	3 (4%)	2 (4%)	1 (4%)
Psudoexfoliation	8 (11%)	6 (12%)	2 (7%)
Juvenile	5 (7%)	5 (10%)	0
Previous ocular surgery or trauma	0	0	0
Preoperative glaucoma medications	76 (100%)	49 (100%)	27 (100%)
One	12 (16%)	11 (22%)	1 (4%)
Two	35 (46%)	21 (43%)	14 (52%)
Three	25 (33%)	13 (27%)	12 (44%)
Four	4 (5%)	4 (8%)	0
Average IOP (mm Hg), mean ± SD	30 ± 8	31 ± 9	28 ± 6
Visual acuity,*			
Mean ± SD	0.68 ± 0.30	0.78 ± 0.24	0.50 ± 0.30
Range	1.00-0.03	1.00-0.05	1.00-0.03
Condition of optic disk†			
Normal	3 (4%)	1 (2%)	2 (7%)
Early glaucomatous cupping	30 (39%)	25 (51%)	5 (19%)
Advanced glaucomatous cupping	43 (57%)	23 (47%)	20 (74%)
Condition of visual field*			
Normal	14 (18%)	12 (24%)	2 (7%)
Early glaucomatous defect	25 (33%)	21 (43%)	4 (15%)
Advanced glaucomatous defect	37 (49%)	16 (33%)	21 (78%)

*Significant difference between procedures, P<.001.
†Significant difference between procedures, P<.025.

had undergone additional surgery (except the eye of one patient in the partial-thickness group who had aspiration of a postoperative hyphema). Statistically significant (P<.05) differences in the mean intraocular pressures was present at one year (Table 4). Although the incidence of complications was higher in the full-thickness group, the difference between the two groups was not statistically significant.

Some of the patients' eyes were reexamined one year or more after the procedure. The pressure difference between the two groups that was evident during the early postoperative period persisted beyond one year (Fig. 2).

The scatter and range of the full-thickness group was increased by one case of extreme hypotony in which pressure was recorded as zero. However, this case alone did not account for the differ-

TABLE 2

IMMEDIATE POSTOPERATIVE CHARACTERIZATION OF EYES

Condition	Total Eyes (No. = 76)	Group: Partial-Thickness Procedure (No. = 49)	Group: Full-Thickness Procedure (No. = 27)
Anterior chamber depth*			
Shallow	5 (7%)	1 (2%)	4 (15%)
Flat	14 (18%)	2 (4%)	12 (44%)
Requiring reformation	0	0	0
Hyphema			
Small	36 (47%)	20 (41%)	16 (59%)
Large	1 (1%)	1 (2%)	0
Requiring aspiration	1 (1%)	1 (2%)	0
IOP (mm Hg)†			
Mean ± SD	14 ± 9	14 ± 9	15 ± 9
Range	4-43	4-43	5-28

*Significant difference between procedures, P<.001.
†Inpatient intraocular pressures were recorded for only 28 of 76 eyes.

ence in pressure of the two groups. In the full-thickness group, 12 out of 27 eyes (44%) were clustered in range of 6 to 14 mm Hg, while the same number out of 49 eyes (24%) were in this range in the partial-thickness group.

DISCUSSION

The data of this study indicate that partial- and full-thickness filtration procedures differ significantly in three respects. The partial-thickness procedures produce a higher final pressure, a lower

TABLE 3

CHARACTERIZATION OF EYES THREE TO 12 WEEKS AFTER SURGERY

Condition	Total Eyes (No. = 76)	Group: Partial-Thickness Procedure (No. = 49)	Group: Full-Thickness Procedure (No. = 27)
Visual acuity*, decimal			
Mean ± SD	0.71 ± 0.30	0.81 ± 0.24	0.53 ± 0.34
Range	1.00-0.03	1.00-0.05	1.00-0.03
% Change (compared with preoperative)	+4	+4	+6
IOP (mm Hg)†			
Mean ± SD	17 ± 6	18 ± 6	15 ± 6
Range	5-39	6-39	5-27
Filtration bleb‡			
Present	37 (49%)	18 (37%)	19 (70%)
Absent	23 (30%)	23 (47%)	0
Not recorded	16 (21%)	8 (16%)	8 (30%)
Early postoperative problems			
Increased IOP	8 (11%)	5 (10%)	3 (11%)
Rapid forming cataract	1 (1%)	0	1 (4%)

*Not recorded at this time in five eyes.
†Significant difference between procedures, P<.05.
‡Significant difference between procedures, P = .005.

TABLE 4

CHARACTERIZATION OF EYES ONE YEAR AFTER SURGERY

Condition	Group		
	Total Eyes (No. = 76)	Partial-Thickness Procedure (No. = 49)	Full-Thickness Procedure (No. = 27)
Visual acuity*,			
Mean ± SD	0.67 ± 0.34	0.76 ± 0.29	0.49 ± 0.35
Range	1.00-0.02	1.00-0.02	1.00-0.02
% Change (compare with preoperative)	−2	−3	−2
IOP†‡ (mm Hg)			
Mean ± SD	16 ± 4.9	17 ± 3.8	15 ± 5.9
Range	0-29	9-29	0-24
Postoperative glaucoma agents			
None	62 (82%)	40 (82%)	22 (81%)
One	6 (8%)	4 (8%)	2 (7%)
Two	8 (10%)	5 (10%)	3 (11%)
Postoperative problems§			
Cataract	3 (4%)	2 (4%)	1 (4%)
IOP pressure >24 mm Hg	10 (13%)	5 (10%)	5 (19%)
Acute idiopathic iritis	2 (3%)	1 (2%)	1 (4%)
Macular pucker	1 (1%)	0	1 (4%)
Bleb infection	1 (1%)	0	1 (4%)
Total	17 (22%)	8 (16%)	9 (33%)

*Vision not recorded in three eyes at one year.
†Significant difference between procedures, $P<.05$.
‡A few data in each group obtained beyond one-year follow-up.
§Other than field loss.

incidence of flat anterior chambers, and a lower incidence of recognizable filtration blebs.

Our present sample size was too small to determine which procedure was followed by fewer complications. Our data suggest that this partial-thickness procedure does not solve the problems during the postoperative period for open-angle glaucoma. We believe that a larger sample size would result in significant differences in the number of complications between procedures.

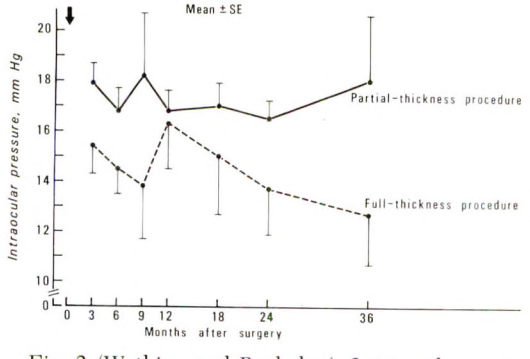


Fig. 2 (Watkins and Brubaker). Intraocular pressures (M ± SE) in eyes after filtration surgery.

SUMMARY

We compared the results of partial-thickness (trabeculectomy) vs full-thickness (trephine) filtration surgery when used as the primary surgical treatment of medically uncontrolled open-angle glaucoma. Prospectively acquired data were used from a series of patients who were examined and operated on by one surgeon. Both groups of data were gathered consecutively and concurrently. The choice of operation was made on the basis of the pressure level required for control of the glaucoma, the full-thickness procedure being chosen for

PATHOLOGY OF PARS PLANITIS

JONATHAN E. PEDERSON, M.D., KENNETH R. KENYON, M.D.,
W. RICHARD GREEN, M.D., AND A. EDWARD MAUMENEE, M.D.
Baltimore, Maryland

The syndrome of chronic intraocular inflammation characterized by an externally quiet eye, minimal anterior-chamber reaction, anterior vitreous opacities, and a "snowbank" overlying the vitreous base has been variously named peripheral uveitis,[1] pars planitis,[2] cyclitis with peripheral chorioretinitis,[3] chronic cyclitis,[4] and basal uveoretinitis.[5] The disorder affects mainly children and young adults with the insidious onset of "floaters" or hazy vision, often bilaterally. Edema of the optic disk and macula, together with dilated and occasionally sheathed retinal veins occurs frequently.[6] Fluorescein angiography of 39 eyes with pars planitis has revealed patchy staining of major retinal veins in all cases and macular edema in 65% of cases.[7]

This condition must be clinically differentiated from acute and chronic nongranulomatous iridocyclitis, nematode endophthalmitis, aphakic macular edema, peripheral toxoplasmosis, sarcoidosis, and Behçet's syndrome.[6]

Pars planitis may have a benign course, but about one half of the cases result in complications of cataract, glaucoma, or retinal detachment. Usually, the more severe the inflammation, the worse the prognosis.[8] Several treatments such as diathermy,[9] cryotherapy,[10] and corticosteroids have been used with varying results. Antimetabolites have been effective in a few cases.[11,12] The cause is entirely unknown. The pathogenesis has been variously attributed to a primary inflammation of the vitreous,[13] retinal vessels,[6] or ciliary body,[4] or to a diffuse uveitis, or to an immune reaction at the vitreous base.[14] However, uveitis surveys in these patients are always unrevealing.

Pathologic studies in pars planitis have been limited to seven previously published cases.[4,6,15] This report presents the histopathology of seven additional cases in various stages of pars planitis. In two cases transmission electron microscopy was performed to determine the composition and possible origin of both the "snowbank" opacity overlying the pars plana and the adjacent epiretinal membranes.

CASE REPORTS

Case 1—A 51-year-old man was first seen in February 1968 with a five-year history of blurred vision in the left eye.[16] Intraocular pressure (IOP) was 18 mm Hg in the right eye and 55 mm Hg in the left eye. Examination showed a few small keratic precipitates, heterochromia, and a few vitreous cells in the left eye. In both eyes a typical "snowbank" of the vitreous base, overlying the pars plana inferiorly, was visible. A thorough medical evaluation was unrevealing. In August 1968, cyclocryotherapy was applied over the inferior 180 degrees of the left eye. Later, a cataract developed in the left eye and an intracapsular extraction with cautery of the wound was performed, with postoperative acuity correctable to 6/6 (20/20). In September 1972, however, vision in the left eye was no light perception with total glaucomatous cupping. Fluorescein angiography showed mild leakage of dye from the nerve head and mural staining of the retinal veins of the affected eye. Because of pain, the left eye was removed in August 1973.

Gross examination revealed that moderately dense, white opacification of the vitreous base overlay the pars plana and ora serrata inferiorly (Fig. 1). Light microscopy showed the angle partially closed with peripheral anterior synechia. The iris was unremarkable except for a mild inflammatory cellular infiltrate consisting mainly of plasma cells and some lymphocytes. In the ciliary body, the pars plicata contained a few chronic inflammatory foci and mild

From the Eye Pathology Laboratory of the Wilmer Ophthalmological Institute, Johns Hopkins Medical Institutions, Baltimore, Maryland. This study was supported in part by Postdoctoral National Research Service Award 1 F32 EY 05133-01 (Dr. Kenyon), and Research Grant 1 RO1 EY 01684-02 (Dr. Green), from the National Eye Institute.

Reprint requests to W. Richard Green, M.D., Eye Pathology Laboratory, Wilmer Institute, Johns Hopkins Hospital, Baltimore, MD 21205.

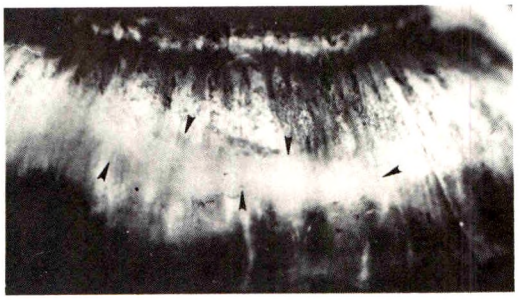


Fig. 1 (Pederson and associates). Case 1. On gross examination, "snowbank" of the vitreous base (arrowheads) overlies the pars plana and ora serrata inferiorly (×10).

glaucomatous flattening. The middle and anterior portions of the pars plana and the posterior aspect of the pars plicata showed thinning and, in some areas, atrophy of the pigmented ciliary epithelium. (These changes presumably resulted from the cyclocryotherapy.) Overlying the pars plana was a thick, moderately dense connective tissue containing a few small vessels emanating from the retina, cells that appeared to be fibrocytes, hyperplastic nonpigmented ciliary epithelium and a few scattered mononuclear inflammatory cells (Figs. 2 and 3). The peripheral retina had been drawn anteriorly and was continuous with the vitreous "snowbank." The retina showed widespread glaucomatous atrophy with marked glaucomatous cupping of the optic nerve head. Some secondary and tertiary branches of the central retinal vein showed prominent mural infiltration by lymphocytes (Fig. 4), without involvement of the retinal arterioles. Discontinuity of the

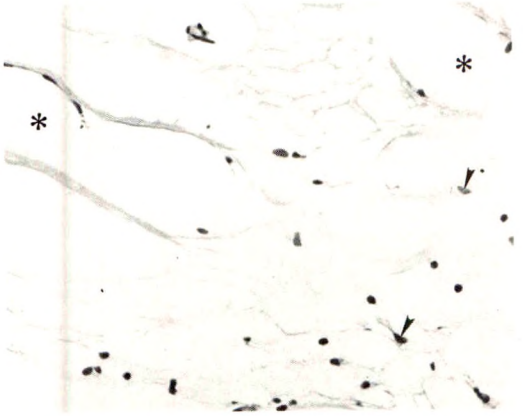


Fig. 3 (Pederson and associates). Case 1. Vitreous "snowbank" opacity with spindle-shaped cells (arrowheads), small blood vessels (asterisks) and lymphocytic infiltration (hematoxylin and eosin, ×500).

internal limiting membrane was present in several areas adjacent to large retinal vessels, and in some instances there was direct contribution of retinal glial cells to the thin preretinal membrane that, in the periphery, became continuous with the intravitreal "snowbank." Electron microscopy showed that the fibrovascular tissue immediately overlying the pars plana consisted of well-differentiated capillaries with continuous, nonfenestrated endothelial linings, invested by basement membrane and peritheli-al cells (Fig. 5). Interspersed among these vessels were loose, randomly oriented aggregates of fibrils with uniform small diameter (about 12 to 14 nm), resembling condensed vitreous material. Additional

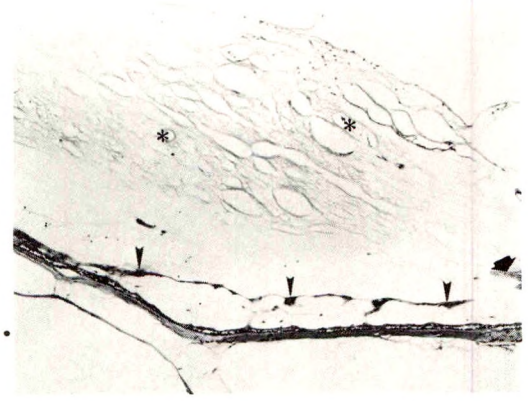


Fig. 2 (Pederson and associates). Case 1. "Snowbank" composed of vitreous condensate, blood vessels (asterisks), scattered lymphocytes, spindle-shaped cells, and proliferated nonpigmented ciliary epithelium (arrowheads) (peripheral retina, arrow) (hematoxylin and eosin, ×100).

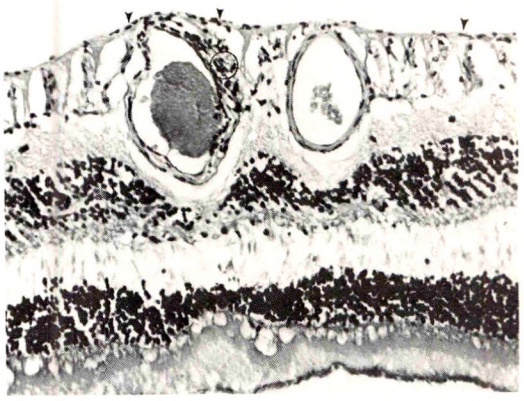


Fig. 4 (Pederson and associates). Case 1. Posterior retina shows a moderately intense infiltration of wall of vein by lymphocytes (circled). Adjacent arteriole is not affected. A thin preretinal fibrous layer (arrowheads) overlies the internal limiting membrane (hematoxylin and eosin, ×235).

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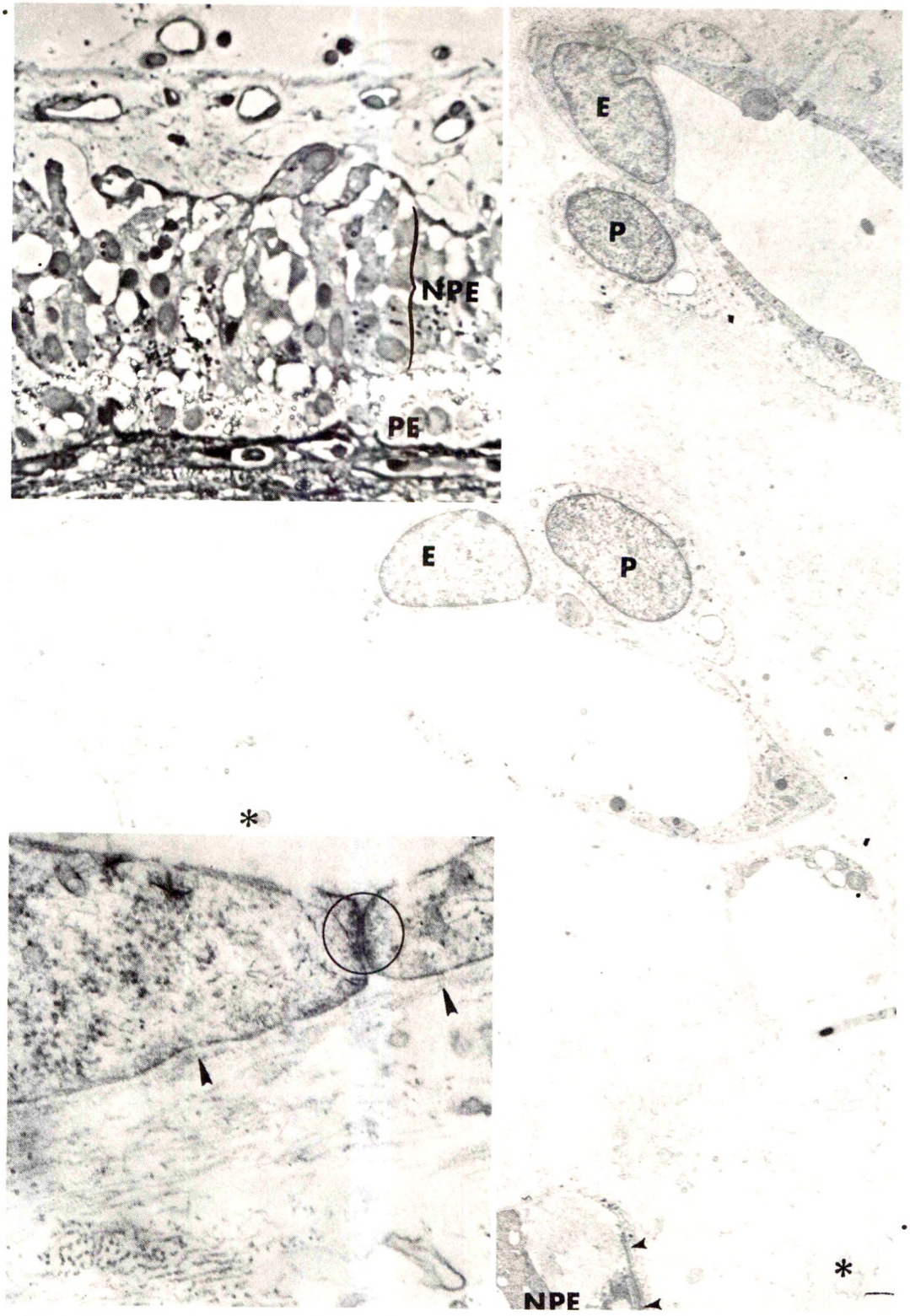


Fig. 5 (Pederson and associates). Case 1. Inset (above): light micrograph of pars plana shows uniform pigmented ciliary epithelial layer (PE), hyperplastic nonpigmented ciliary epithelium (NPE), and overlying fibrous tissue with numerous small vessels (phase contrast, paraphenylenediamine, ×1,000). Main figure is electron micrograph of this fibrovascular tissue including base of nonpigmented epithelium (NPE) with basement membrane (arrowheads), scattered membranous fragments (asterisks), loosely aggregated fibrils, and capillary with continuous endothelial lining (E) and adjacent perithelial cell (P) (×27,000). Inset (below): at higher magnification, the junctions (circled) between vascular endothelial cells (E), and the endothelial basement membrane (arrowheads) are visible. The adjacent fibrils uniformly measure between 12 to 14 nm in diameter, resembling condensed vitreous (×74,000).

extracellular material, including membranous fragments and cytoplasmic debris, was scattered throughout this area.

• The more vitreal portion of the "snowbank" was different, being avascular and consisting of elongated fibrocyte-appearing cells with thin processes interposed among collagenous aggregates. These cells had the characteristics of fibrous astrocytes, as their cytoplasm contained abundant microfilaments (about 7 to 8 nm diameter) and dilated cisternae of rough-surfaced endoplasmic reticulum (Fig. 6.). The cells also had numerous desmosomal attachments and extensive junctional complexes, and had produced almost complete basement membranes (Fig. 7). The cells did not contain pigment granules. The extracellular collagenous material, which presumably had been produced by these astrocyte-like cells, differed from vitreous fibrils because they were of larger diameter (about 24 nm) with the longitudinal macroperiodicity typical of native collagen (about 60 nm) (Fig. 8).

The preretinal membrane extending over the posterior retina was ultrastructurally similar to that of the vitreous "snowbank" in cellular and collagenous composition. The endothelial junctional complexes of the retinal capillaries and larger vessels appeared intact, and no abnormalities were present other than basement membrane thickening consistent with the age of the patient.

Case 2—A 16-year-old girl was first seen in June 1968 with a history of bilateral uveitis since the age of 8 years.[6] Three glaucoma operations in the left eye were unsuccessful, and the blind and painful eye was enucleated in September 1967. She had also had two glaucoma operations in the right eye, with control of IOP. Examination in June 1968 showed visual acuity of 6/24 (20/80) and IOP of 18 mm Hg in the right eye. A few old keratic precipitates, early band keratopathy, posterior subcapsular cataract, and numerous fine vitreous opacities were noted. The retinal veins were dilated to at least twice normal size, and a typical whitish "snowbank" of organized vitreous was present inferiorly over the pars plana. Thorough studies for uveitis revealed no specific cause.

Gross examination revealed that a dense, white opacification of the vitreous base along the pars plana and ora serrata was present inferiorly (Fig. 9). The retina was detached, and the optic nerve head was cupped. Light microscopy showed a mild scattering of lymphocytes and a few plasma cells present in the iris and ciliary body. The vitreous was detached posteriorly and markedly collapsed so that only a small portion remained. The formed vitreous

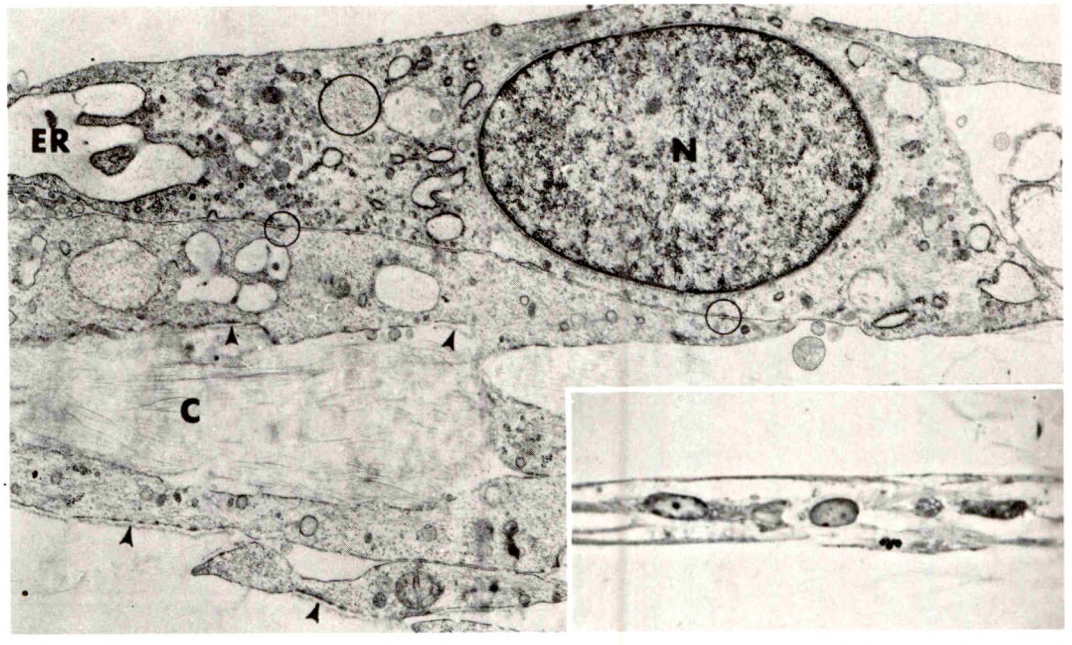


Fig. 6 (Pederson and associates). Case 1. Inset, Light micrograph of intravitreal "snowbank" opacity includes elongated, fibrocytic-appearing cells within a fibrous matrix (phase contrast, paraphenylenediamine, ×1,200). Electron micrograph of this region shows cytoplasmic characteristics of these cells to include numerous, fine microfilaments (large circles), dilated cisternae of rough-surfaced endoplasmic reticulum (ER), prominent nucleus (N), and desmosomal connections (small circles). Extracellularly, these cells display incomplete basement membranes (arrowheads) and have secreted extensive arrays of fibrillar collagen (C) (×24,500).

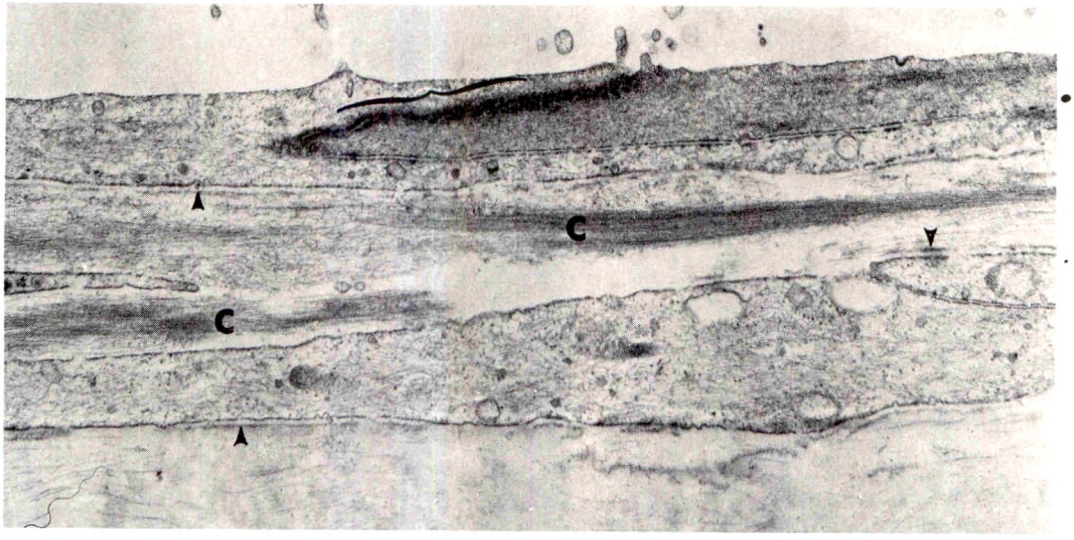


Fig. 7 (Pederson and associates). Case 1. Electron micrograph of presumed fibrous astrocyte within vitreous "snowbank" includes well-developed intercellular junctional complexes (bracketed), cytoplasmic microfilaments, basement membranes (arrowheads), and densely matted collagen (C) (×18,200).

extended anteriorly from the ora serrata on both sides, almost to the posterior surface of the lens. The vitreous contained a light scattering of lymphocytes. Inferiorly, the remaining formed vitreous had a dense aggregation of collagenous tissue in which there were strands of proliferated nonpigmented ciliary epithelium, spindle-shaped fibrocyte-like cells, a few lymphocytes, and occasional thin-walled blood vessels (Fig. 10). This mass had direct continuity with the peripheral retina, which appeared to have been drawn anteriorly past the ora serrata and partially incorporated into this mass. Glia-like cells also extended from the retina into the "snowbank" area. Occasional small aggregates of lymphocytes were present in the choroid. The retina was intact except for prominent glaucomatous atrophy of the nerve-fiber and ganglion-cell layers. Near the posterior pole, there were edematous changes in the outer plexiform and inner nuclear layers. The peripheral retina extending from the midperiphery to the ora serrata had a thickened appearance and a diffuse glial hypercellularity with near-total loss of lamellar structure. There was a mild lymphocytic infiltration in the wall of some of the secondary and tertiary branches of the central retinal vein. There were sporadic areas of preretinal membrane forma-

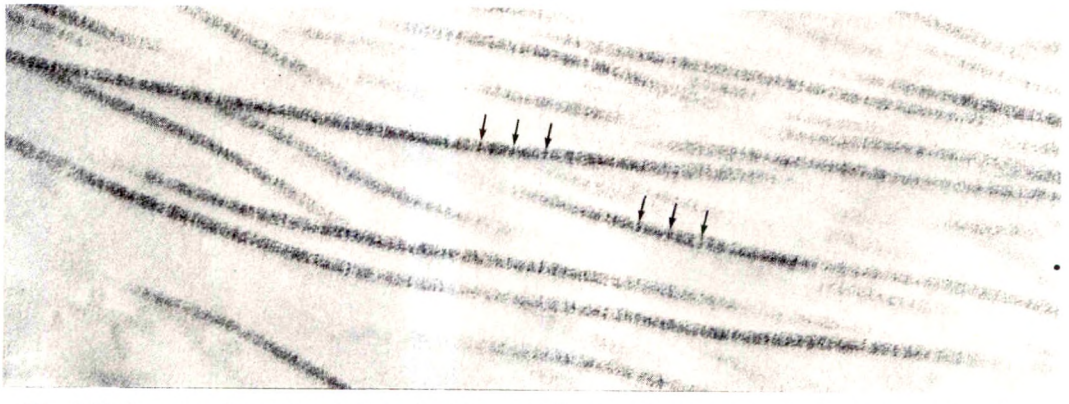


Fig. 8 (Pederson and associates). Case 1. High magnification electron micrograph discloses the collagen fibrils to have a diameter of about 24 nm and about 60 nm longitudinal macroperiodicity (×93,500).

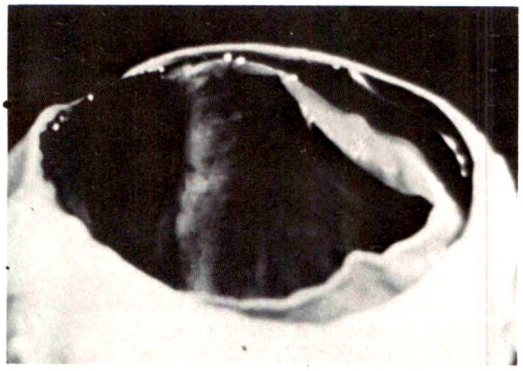


Fig. 9 (Pederson and associates). Case 2. Gross appearance of vitreous "snowbank" over pars plana and peripheral retina.

tion that were occasionally associated with discontinuities of the internal limiting membrane near larger retinal vessels.

Case 3—A 50-year-old woman, with a four-year history of blurred vision and spots before both eyes, had been treated intermittently for posterior uveitis with systemic corticosteroids for one year.[6] In October 1967 visual acuity was R.E.: 6/21 (20/70) and L.E.: 6/30 (20/100), and in both eyes the IOP was normal. Both eyes had minimal aqueous flare, occasional aqueous cells, a few keratic precipitates, and moderate vitreous cells and debris. Cystoid macular edema and vitreous deposits on the peripheral retina were present in both eyes. In February 1968, visual acuity was R.E.: 6/90 (20/300) and L.E.: 6/60 (20/200). Vitreous opacities were seen over the peripheral retina from 8 to 11 o'clock in the right eye and 2 to 5 o'clock in the left eye. Angiography showed cystic pooling of fluorescein in both maculas. The diagnosis was pars planitis; the patient was given prednisone, 80 mg a day. By May 1968, visual acuity had improved to 6/18 (20/60) in each eye, and corticosteroids were reduced to 20 mg a day during the next month. On June 11 she developed motor instability and headache, then became acutely ill and died two days later. Autopsy revealed a pulmonary abscess and multiple cerebral and cerebellar abscesses from which *Nocardia* was cultured.

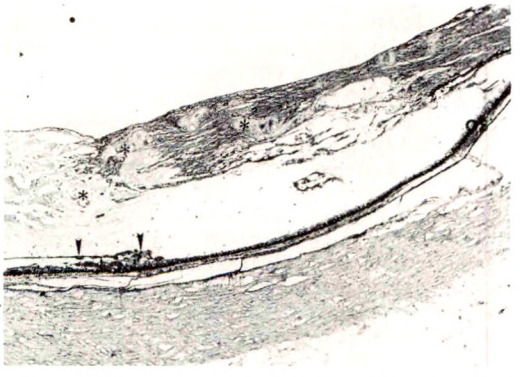


Fig. 10 (Pederson and associates). Case 2. Near-total collapse of vitreous with "snowbank" composed of condensed vitreous, blood vessels (asterisks), lymphocytes, proliferated nonpigmented ciliary epithelium (arrowheads). Fibrogliotic peripheral retina has been pulled forward over pars plana and retinal glial cells have proliferated into the "snowbank" (ora serrata, 0 S) (hematoxylin and eosin, ×50).

On gross examination the eyes appeared normal. Light microscopy showed similar histopathologic features present in each eye. The cornea and angle structures were normal, and the iris and ciliary body and choroid were free of inflammation. The vitreous was detached posterior to the equator, contained a few lymphocytes, and was condensed over the pars plana, with slight traction on the peripheral retina. The retina was unremarkable except for occasional areas of mild phlebitis and cystoid macular edema.

Case 4—A 42-year-old woman was first seen in August 1962. At age 20, she had been told of iritis in her left eye; within six months she developed acute glaucoma, and underwent an iridectomy of the left eye. Injections of ACTH did not improve vision. The eye painlessly deteriorated to no light perception in 1957. Examination in August 1962 revealed visual acuity of 6/4.5 (20/15) in the right eye. Intraocular pressure was 17 mm Hg in the right eye and 62 mm Hg in the left eye. Early band keratopathy, moderate aqueous flare without cells, a dense cataract, and extensive peripheral anterior synechiae were noted in the left eye. A few vitreous cells were seen in the right eye. A white, fluffy elevated tissue was present in the right eye overlying the pars plana at 7 o'clock. In December 1963, a mound of angiomatous dilated vessels was visible at the ora serrata at 6 o'clock in the right eye. In May 1964, diathermy was applied to this area with resultant scarring and closure of the vessels. In 1970, she had a short episode of episcleritis in the right eye. In July 1973, severe tearing and pain developed in the left eye, and the eye was removed in October 1973.

Gross examination revealed that the globe did not transilluminate. The anterior chamber was filled with clear yellowish material. Light microscopy showed that the corneal stroma was thickened and vascularized. The angle was closed by peripheral anterior synechiae and fibrous tissue proliferation. The anterior chamber was filled with an eosinophilic fluid. A dense cyclitic membrane was present and was continuous with the totally detached, thickened, and gliotic retina. Overlying the pars plana inferiorly was a dense collagenous tissue, containing cords of proliferated ciliary epithelium and some blood vessels. This tissue was continuous with the markedly gliotic retina, which was drawn forward. Extensive bone was present along the inner

aspect of Bruch's membrane. The choroid was congested and the optic nerve was atrophic.

Case 5—A 34-year-old woman was first seen in July 1969 with a 17-year history of uveitis, mainly affecting the left eye, that had been treated intermittently with systemic and topical corticosteroids. Uveitis testing was unrevealing. In 1963, visual acuity was R.E.: 6/9 (20/30) and L.E.: 6/24 (20/80). In the right eye, moderate-size keratic precipitates were present with trace anterior chamber reaction and a few cells in the anterior vitreous. In the left eye, fine keratic precipitates, moderate flare and cell, advanced posterior subcapsular cataract, and moderate vitreous cellular reaction were evident. The fundus of the right eye showed venous engorgement and vitreous exudate in the peripheral retina and ora serrata inferiorly. In the left eye the retinal veins appeared engorged, a white sheet-like vitreous exudate extended over the inferior half of the retina from the midperiphery, and the macula was edematous. Peripheral angiomatous masses were also noted in the left eye from 5 to 8 o'clock. Transscleral diathermy of these lesions was performed.

In February 1969, iris bombé of the left eye was relieved by sector iridectomy. In May 1969, a hypermature cataract of the left eye was extracted and the vitreous face was observed to be hazy. Iris bombé recurred with increased IOP, and two peripheral iridectomies were performed; however, iris bombé again developed, requiring incision of the lower iris and vitreous. In July 1969, visual acuity was R.E.: 6/7.5 (20/25) and hand motions temporally in the left eye. Intraocular pressure was 14 mm Hg in the right eye and 6 mm Hg in the left eye. The vitreous was vascularized and fibrotic in the left eye, and in the right eye sheathing of the retinal vessels and a typical "snowbank" of organized vitreous inferiorly were observed. Fluorescein angiography of the right eye was unremarkable. The left eye was removed in February 1970.

Gross examination revealed that the globe did not transilluminate and the retina was detached. A dense yellowish-gray mass was present over the pars plana inferiorly, and a dense whitish cyclitic membrane extended transversely. Light microscopy showed the cornea was thickened and irregular, with a dense posterior collagenous layer. A healed scar was present at the superior corneoscleral limbus. The angle was closed with peripheral anterior synechiae, and the anterior chamber was filled with a serosanguineous material. The lens was absent. A dense cyclitic membrane, continuous with a fibrovascular membrane overlying the iris, had drawn the ciliary processes forward. The ciliary body was infiltrated with a mild number of polymorphonuclear leukocytes and lymphocytes. The choroid showed an occasional small focus of lymphocytes. The retina was totally detached and histologically disorganized, and was thickened peripherally where it merged with the cyclitic membrane. In the pars plana region the retina was drawn forward, was gliotic, and was infiltrated with a moderate number of lymphocytes.

Case 6—A 9-year-old girl had an unremarkable ocular history before decreased vision in her right eye was found during a routine school vision test. Ophthalmologic examination showed a dense, white vitreous mass temporally. The patient denied trauma and stated that the right eye had never been red or painful.

On initial examination in January 1976, visual acuity was R.E.: 5/400 (20/1600); and L.E.: 6/7.5 (20/25). In the right eye, an afferent pupillary defect, a 3+ vitreous cellular reaction, and IOP of 12 mm Hg were noted. Ophthalmoscopic examination showed clouding of the media and definite swelling of the right optic nerve head, with some distortion from vitreous traction extending inferiorly toward a peripheral white mass over the pars plana inferiorly from 5 to 7 o'clock. Three months later, visual acuity in the affected right eye was still about 5/200 (20/800) although the media were consistent with visual acuity of about 6/18 (20/60) and numerous opacities moved freely within the formed vitreous gel. The optic nerve head and macula were edematous. At a six-month follow-up examination, visual acuity was unchanged in each eye, and in the right eye the quality of media still exceeded the vision. Slit-lamp examination showed a 3+ level of cells in the vitreous of the right eye, and 1+ vitreous cells in the left eye. With indirect ophthalmoscopy, a preretinal membrane could be traced inferiorly from the disk. In the left eye, a definite white exudate over the inferior pars plana region was apparent, suggesting the diagnosis of pars planitis.

In October 1976, visual acuity was reduced to 3/200 (20/1320) in the right eye but remained at 6/7.5 (20/25) in the left eye. Fundus examination of the right eye revealed heavy vitreous debris overlying the entire posterior retina, with preretinal membrane formation over the optic nerve and extending inferiorly. An increase in the peripheral exudative change was evident also in the left eye. A pars plana vitrectomy combined with transscleral cryotherapy to the inferior pars plana area and partial dissection of the peripapillary preretinal membrane were performed in the right eye. During the 15-month follow-up, visual acuity in the right eye remained at 3/200 (20/1320) and in the left eye at 6/9 (20/30 +1). Although 1+ vitreous cells persisted in the right eye, the media were clear. There was some residual preretinal membrane on the nerve head and retina inferiorly. Adequate cryotherapy reaction surrounded a peripheral traction detachment. The residual "snowbank" over the inferior pars plana appeared to undergo involution. No changes were evident in the left eye. On light microscopy the material from the vitreous aspirate, concentrated by Millipore filtration and stained with a modified Papanicolaou technique, showed numerous epithelioid mononuclear cells and lymphocytes with some multinuclear giant cells. No eosinophils were seen. A few large fibroblast-like cells were present. Several larger tissue fragments from the preretinal membrane were prepared for transmission electron microscopy. This material was composed mainly of large fusiform cells with numerous interdigitating cellular processes, arranged in multiple layers (Fig. 11). The nuclei of these cells were large and ovoid with some peripheral margin of chromatin. The major cytoplas-

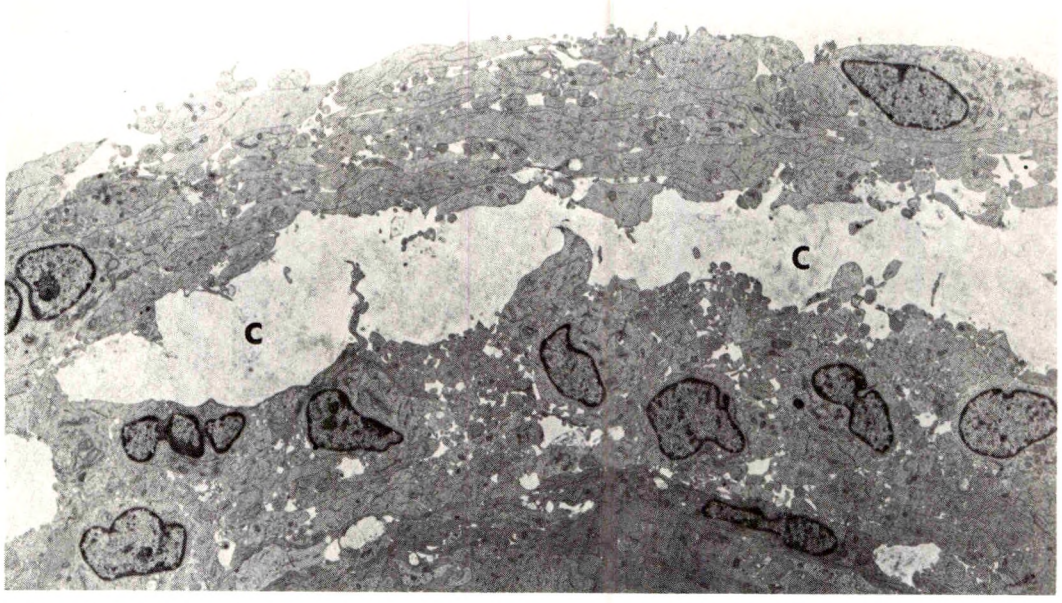


Fig. 11 (Pederson and associates). Case 6. Survey electron micrograph of vitrectomy specimen shows an extremely cellular proliferation consisting of fusiform cells with elaborately interdigitated processes and relatively small quantities of extracellular collagen fibrils (C) (×3,000).

mic component, especially in the cellular processes, was abundant microfilaments (about 7 to 8 nm diameter), with moderate amounts of glycogen particles and rough-surfaced endoplasmic reticulum also present (Fig. 12). At higher magnification, basement membrane and intercellular junctions of both gap and desmosome types were evident. Only small amounts of fibrillar collagen were evident in the extracellular spaces, and these fibrils measured about 12 to 14 nm diameter, characteristic of vitreous collagen. No blood vessels or inflammatory cells were seen.

Case 7—A 44-year-old man first noted dim vision in the left eye as a child, but this was asymptomatic until he was 36 years old in 1952. For the next eight years the patient had a recurring red, painful left eye. In 1958, the patient was told he had glaucoma and iritis of the left eye, which soon became blind. In January 1960, examination of the left eye showed no light perception and an IOP of 72 mm Hg. The left cornea was edematous and had keratic precipitates, and there was also a marked anterior chamber flare and cell. Rubeosis iridis was noted, with posterior synechiae from 6 to 11 o'clock. The lens was densely opacified, and the retina could not be seen. The right eye was normal. On Jan. 11, 1960, the left eye was enucleated. Final examination of the right eye in 1965 showed no abnormality.

Gross examination revealed that the globe was unremarkable except for an opaque thickened tissue over the ora serrata. Light microscopy showed fibroinflammatory pannus extending onto the cornea for a short distance. Nasally, descemetization of the anterior angle was present. Temporally, mononuclear inflammatory cells were seen in the trabecular meshwork. The iris and ciliary body had a mild-to-moderate cellular infiltrate of lymphocytes and plasma cells. The vitreous was detached and collapsed, forming a dense collagenous mass at its base anteriorly (Fig. 13). This "snowbank" area was composed of condensed vitreous, fibrocyte-appearing cells and rare blood vessels, and was adjacent to the gliotic and forwardly drawn peripheral retina. A few mononuclear inflammatory cells, and a few cords of nonpigmented ciliary epithelium were also present in this tissue. Glial cells extended from the retina along the inner surface of the collagenous mass for a short distance. A few chronic inflammatory cells were present in the choroid peripherally. The retina showed atrophy of the ganglion-cell and nerve-fiber layers. Some retinal veins were infiltrated with lymphocytes (Fig. 14).

Discussion

These cases illustrate the complications that may occur with long-standing pars planitis: (1) cystoid macular edema; (2) vitreous opacification, detachment, and condensation; (3) cataract; (4) neovascularization of vitreous base; (5) rubeosis iridis; (6) heterochromia iridis; (7) glaucoma; (8) preretinal membrane; (9) retinal detachment; (10) band keratopathy; (11)

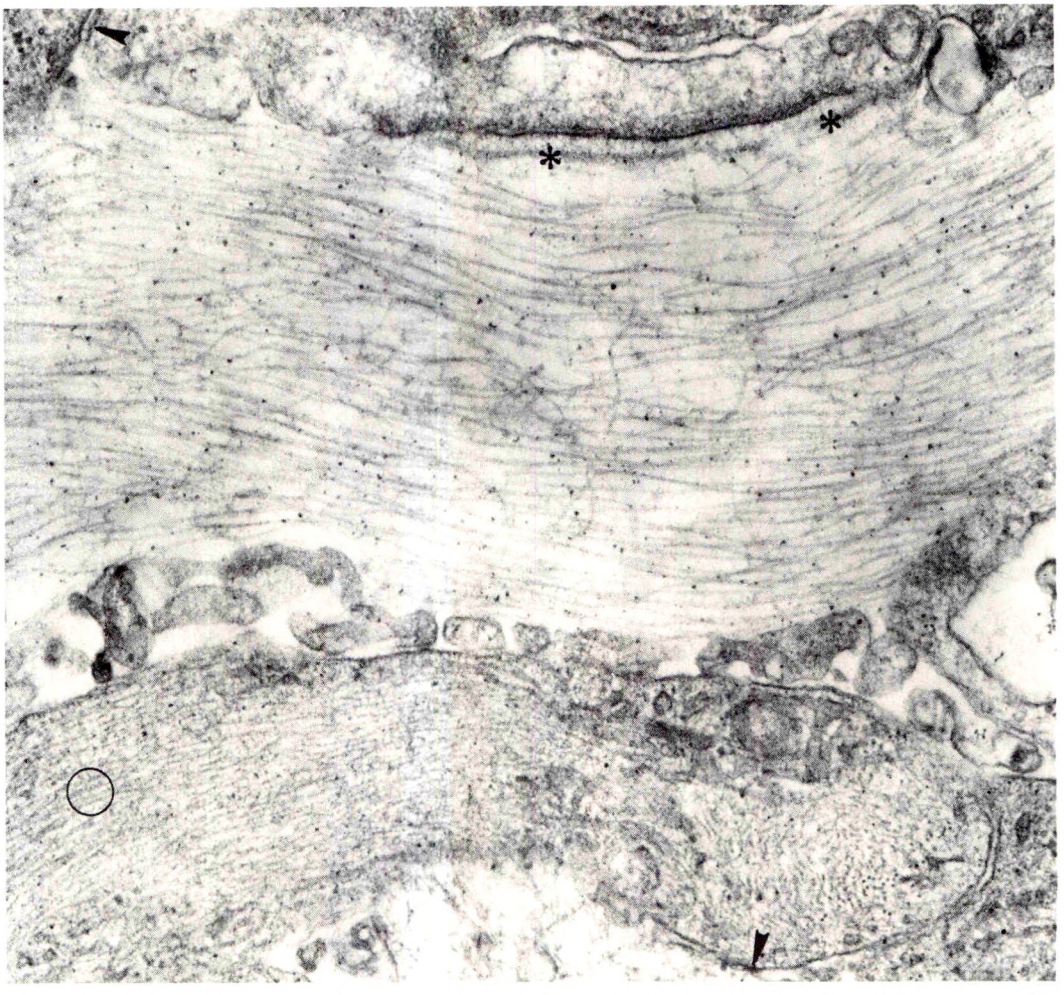


Fig. 12 (Pederson and associates). Case 6. At higher magnification, these cells exhibit innumerable intracytoplasmic microfilaments (7 to 8 nm diameter) (circled), intercellular gap, and desmosomal junctions (arrowheads), segmental basement membrane, and masses of vitreouslike fibrillar collagen (about 12 nm in diameter) (×42,000).

cyclitic membrane; and (12) phthisis bulbi. In the five enucleated eyes, glaucoma, cataract, and phthisis bulbi were common, whereas in the two autopsy eyes (Case 3) and one vitrectomized eye (Case 6) only cystoid macular edema had also developed.

The histopathologic features of these cases include detachment and collapse of the vitreous body with fibrous organization of the vitreous base, chronic inflammatory cells in the vitreous, edema of the optic nerve head and macula, retinal phlebitis and periphlebitis, preretinal membranes associated with breaks in the internal limiting membrane, anterior traction of the peripheral retina, and no significant choroiditis, cylitis, or peripheral chorioretinal atrophy. By contrast in the three cases reported by Brockhurst, Schepens, and Okamura,[15] (one had fibrous iritis and the other two showed focal areas of peripheral choroiditis consisting of lymphocytes, plasma cells and eosino-

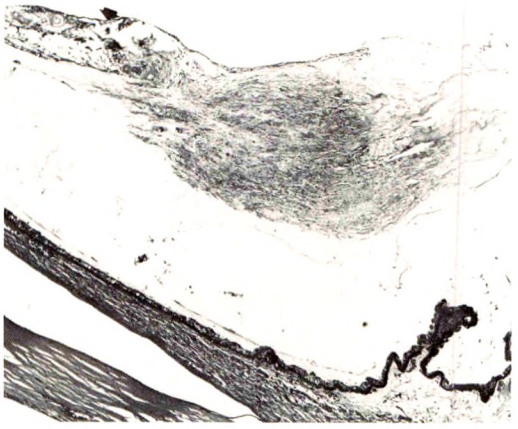


Fig. 13 (Pederson and associates). Case 7. "Snowbank" composed of collapsed and condensed vitreous. Peripheral gliotic retina (arrow) has been pulled forward over the pars plana and is intimately connected with the vitreous "snowbank" (hematoxylin and eosin, ×55).

phils); the case of Kimura and Hogan[4] showed low-grade lymphocytic and plasma cell infiltration of the pars plana and mild diffuse lymphocytic infiltration of the posterior choroid.

The significance of these findings of uveal and vitreal inflammation has been a point of controversy. Because of the lack of histopathologic material in the early stages of the disease, it has not been possible to answer these questions conclusively. In the advanced cases reported here, chronic inflammation of the uveal tract was present, but minimal, and no more than would be expected considering the possible complications of the disease and the effects of multiple surgical procedures. Moreover, in our one patient with a prolonged but rather uncomplicated course (Case 3), the iris, ciliary body, and choroid appeared entirely free of inflammation; and in the vitrectomized eye (Case 6), with recently detected pars planitis, vitreous inflammation was considerable. The fairly mild choroidal or cyclitic inflammation must be interpreted as the sequela of a chronic vitreoretinal inflammatory process, plus the added effect of surgical trauma. A far more intense inflammatory reaction of the uveal tract would be expected if uveal inflammation were to have primarily stimulated the observed reaction in the pars plana. A primary vitreoretinal inflammatory mechanism (possibly immunologic) is also suggested by the experimental production of clinically similar "snowbanks" in owl monkeys receiving multiple intravitreal injections of hyaluronic acid.[17]



Fig. 14 (Pederson and associates). Case 7. Retinal phlebitis with lymphocytes (circled) in wall of tertiary branch of central retinal vein (hematoxylin and eosin, ×200).

The composition and origin of the "snowbank" overlying the pars plana has been previously described as an inflammatory mass (pars plana exudate) or condensed vitreous. The predilection for the "snowbank" to lie inferiorly may be caused by gravitational settling of vitreous opacities on an inflamed vitreous base, but Gärtner[14] suggested it may be because more vitreous cells are normally present in the zonular region inferiorly.

A unique feature of Case 1 is the ultrastructural indication that the pars plana "snowbank" consists not only of a vascularized condensate of vitreous collagen with interspersed chronic inflammatory cells and hyperplastic nonpigmented ciliary epithelium, but also of fibroglial tis-

sue composed of cells that appear to be fibrous astrocytes, and of larger-diameter collagen fibrils presumably secreted by these cells. The extensive involvement of fibrous astrocytes is also emphasized by the ultrastructural findings in Case 6.

Human vitreous collagen fibrils have generally been found to measure between 8 nm and 16 nm in diameter,[18,19] and the 12- to 14-nm fibrils we observed are probably aggregates of vitreous collagen. The vascular components of this tissue probably originate in the peripheral retina, as is suggested by their ultrastructural similarity to well-differentiated retinal or iris capillaries.[20] In Cases 1, 2, and 7, these vessels were continuous with the retina. Neovascularization of the vitreous base can be clinically evident in pars planitis,[6] and the frequent occurrence of focal interruptions in the internal limiting membrane of the peripheral retina at the vitreous base[21,22] may provide easy access of retinal vessels to the overlying vitreous. The significance of membranous and cytoplasmic remnants and debris in this area is not certain. Gärtner[14,23] interpreted such material as being the breakdown products of vitreous and glial cells, and speculated that the auto-antigenic properties of such debris might support an immunologic disease mechanism in pars planitis. We believe such materials are an inconspicuous component of the vitreous "snowbank" and are either an incidental normal occurrence or nonspecific remnants of long-standing inflammation.

The cellular elements of the inner portion of the "snowbank" closely resemble glial cells, especially fibrous astrocytes, and clearly differ from vitreous histiocytes, fibrocytes, retinal pigmented epithelium and macrophages regarding their cytoplasmic microfilaments, intercellular junctions, extracellular basement membranes, and extensive fibrillar collagenous secretion.[19,22,24–27] The distinction between these presumed astrocytes and nonpigmented ciliary epithelial cells is less certain, because both can have similar ultrastructural characteristics, although microfilaments are far more common in the fibrous astrocyte.[28,29] Likewise, the collagenous material observed in Case 1 is easily distinguished from normal vitreous collagen by its larger fibril diameter. Although the retinal fibrous astrocyte has not been proven capable of fibrillar collagen production, the astrocyte is known to be highly reactive following injury of the central nervous system.[30] Fibroglial membranes are ultrastructurally similar to those described in various situations of periretinal fibrous proliferation,[31,32] and are thought to result from metaplasia of retinal pigment epithelial or fibrous astrocytic cells.[31–34] Machemer and Laqua[35] also determined that, in experimental retinal detachments involving the pars plana, continuous preretinal and intravitreal collagenous membranes are produced by glialike cells. Since preretinal membranes of this type were always present in our other pars planitis cases, their development in the vitreous probably represents a similar stimulus for glial cell migration and proliferation. The occurrence of periretinal fibrous proliferations is often associated with chronic inflammation, allowing us to speculate that in pars planitis the development of the fibroglial "snowbank" may be the extension of a common inflammatory process involving both the peripheral retina and vitreous base.

The clinical development of posterior detachment of the vitreous body, and later anterior condensation and collapse, is especially prominent in young patients with pars planitis. Given the greater strength of vitreoretinal attachments in younger persons, it is possible that an inflammation-induced shrinkage of the vitreous may produce traction on the reti-

na, thus accounting both for the vascular instability of cystoid macular edema and for breaks in the internal limiting membrane that would facilitate the preretinal and pars-plana fibrous proliferations.

Summary

Seven eyes and one vitrectomy specimen from seven patients with pars planitis and complications such as secondary glaucoma and phthisis bulbi were studied histopathologically. Two of the specimens were also examined by electron microscopy. All cases showed a typical intravitreal "snowbank" opacity overlying the pars plana. On light microscopy, these "snowbanks" appeared to consist of a loose fibrovascular layer containing occasional fibrocyte-like cells and scattered mononuclear inflammatory cells adjacent to the hyperplastic nonpigmented epithelium of the pars plana. Within the vitreous base, an extensive fibroglial proliferation had developed, often drawing the peripheral retina anteriorly into the "snowbank." Electron microscopy showed this fibroglial tissue to be composed of condensed vitreous collagen and probable fibrous astrocytes which had produced larger-diameter (about 24 mm) collagen fibrils. The fibroglial proliferation also appeared continuous with an ultrastructurally similar preretinal fibroglial membrane. All eyes showed prominent lymphocytic cuffing and mural infiltration of retinal veins, with sparing of the arterioles. Several cases showed cystoid macular edema. Only mild choroiditis or cyclitis could be shown in some cases. We believe that in pars planitis the fibroglial "snowbank" may reflect a common inflammatory process involving both the peripheral retina and vitreous base.

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ACUTE MACULAR NEURORETINOPATHY

IRA. A. PRILUCK, M.D., HELMUT BUETTNER, M.D.,
AND
DENNIS M. ROBERTSON, M.D.
Rochester, Minnesota

In 1975, Bos and Deutman[1] described a newly recognized macular disorder, called acute macular neuroretinopathy. It is characterized by mild visual impairment, paracentral scotomata corresponding to wedge-shaped parafoveal retinal lesions, and normal fluorescein angiography. A single case report of this disorder occurring in the United States was recently published by Rush.[2] We describe herein another case of acute macular neuroretinopathy.

CASE REPORT

A 17-year-old boy came to the Ophthalmology Department of the Mayo Clinic with a two-day history of bilateral central "bluish-green shadows." During the previous week, he complained of flu-like symptoms, including a sore throat and fever. His past medical history was otherwise noncontributory. He had not taken any systemic medications.

Ophthalmic examination revealed visual acuity of 6/6 (20/20) in both eyes. The patient was able to reproduce his bilateral and relative scotomata on the Amsler grid (Fig. 1). External examination, intraocular pressures, and slit-lamp biomicroscopy of the anterior segments and vitreous were normal. Kinetic perimetry confirmed the paracentral defects and showed intact peripheral visual fields (Fig. 2, top). Static perimetry through two of the defects demonstrated dense scotomata (Fig. 2, bottom).

Ophthalmoscopic examination using contact lens biomicroscopy of the right fundus showed an irregular dark appearing disturbance of the deep sensory retina just nasal to the fovea. The left fundus showed similar and more numerous lesions located in the deep sensory retina. These disturbances were best seen by using red-free light (Fig. 3). Except for a small intraretinal hemorrhage located inferior to the left macula, the retinal vasculature, retinal pigment epithelium, and nerve fiber layer were normal in the areas of these lesions.

Fluorescein angiography revealed subtle areas of relative hypofluorescence corresponding to the lesions of the deep sensory retina (Fig. 4). Electrore-

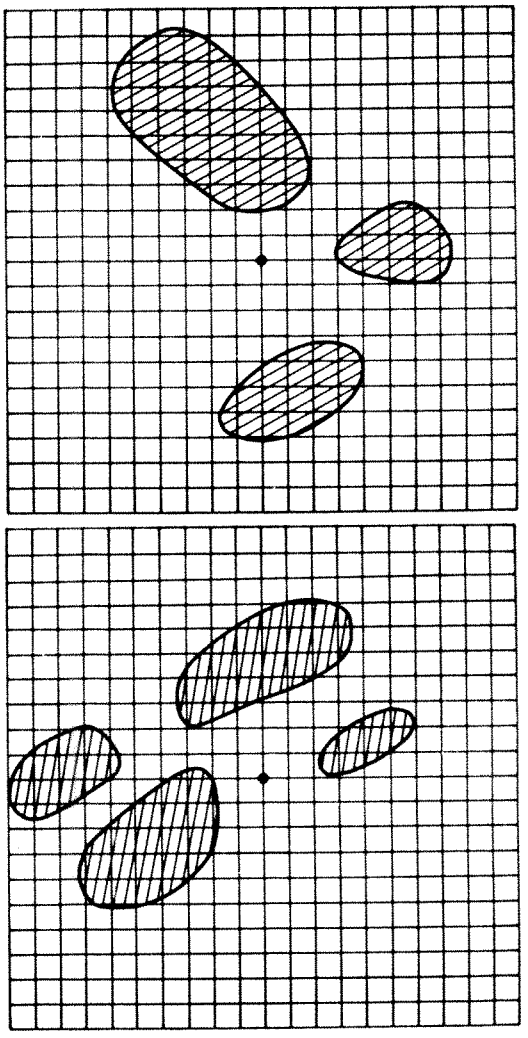


Fig. 1 (Priluck, Buettner, and Robertson). Amsler grid demonstrating parafixational scotomata of right eye (top) and left eye (bottom).

From the Department of Ophthalmology, Mayo Clinic, and the Mayo Medical School, Rochester, Minnesota. This study was supported in part by a Fight for Sight Research Fellowship (Dr. Priluck), Fight for Sight, Inc., New York, New York.

Reprint requests to Ira. A. Priluck, M.D., Creighton University School of Medicine, 601 N. 30th St., Omaha, NE 68131.

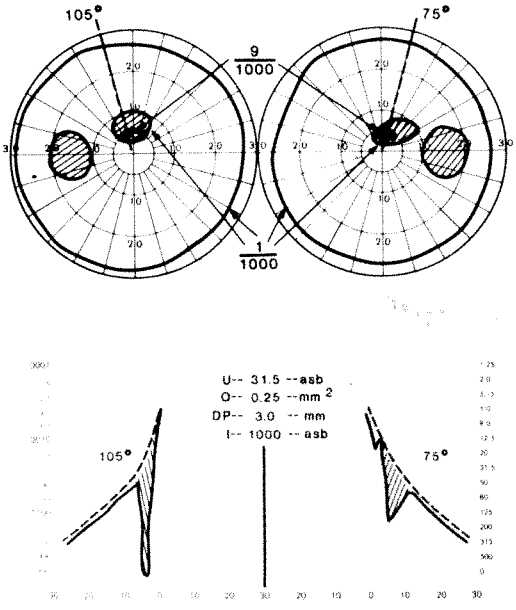


Fig. 2 (Priluck, Buettner, and Robertson) Tangent screen visual field testing (top) and static Goldmann perimetry (bottom) along the 105-degree meridian (left eye) and the 75-degree meridian (right eye) demonstrating dense paracentral scotomata. The dotted line represents the normal static perimetry through the respective meridians.

tinography, electro-oculography, dark adaptometry, and Farnsworth-Munsell color vision testing were all normal.

A follow-up examination three months later revealed persistent paracentral scotomata, greater in the left eye than the right eye. Visual acuity was 6/6 (20/20), both eyes, and defects on Amsler grid testing remained essentially unchanged. Ophthalmoscopic examination revealed the same subtle disturbances of the deep sensory retina, left eye greater than right eye. The previously noted parafoveal intraretinal hemorrhage of the left macula had resolved. Repeat fluorescein angiography again demonstrated the minimal parafoveal areas of hypofluorescence.

Discussion

Our case exhibits all the characteristic ocular findings of acute macular neuroretinopathy as previously described by Bos and Deutman,[1] and Rush.[2] Our patient had a recent history of an upper respiratory infection, presumably of viral origin, and complained of minor visual impairment. Significant ocular findings were limited to wedge-shaped parafoveal lesions radiating peripherally from the macular regions, which corresponded to reproducible paracentral scotomata on the Amsler grid. Both static and kinetic

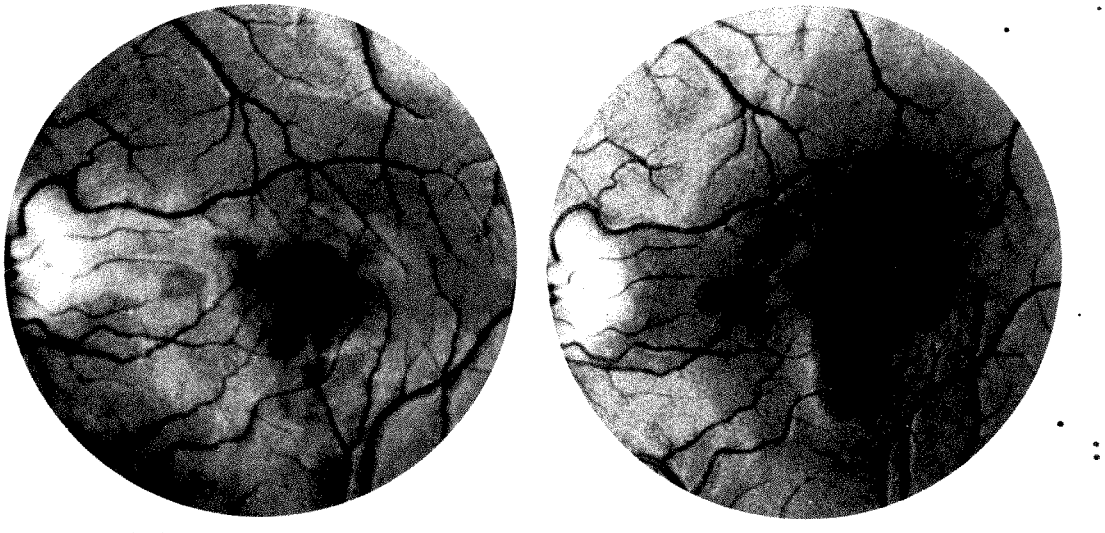


Fig. 3 (Priluck, Buettner, and Robertson). Left eye, Stereoscopic photographs taken with red-free light. Posterior pole shows dark cuneate parafoveal lesions located in the deep sensory retina (viewed best with +7.00 diopter lenses).

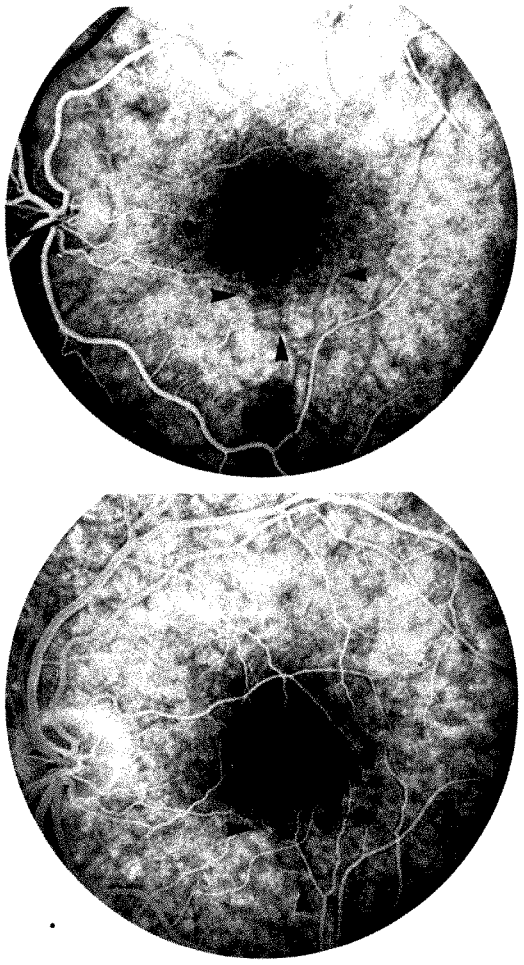


Fig. 4 (Priluck, Buettner, and Robertson). Top, Arterial venous phase of fluorescein angiogram of left eye demonstrates subtle areas of hypofluorescence, which correspond to the disturbance of the deep sensory retina. Bottom, Late venous phase of angiography shows persistence of these hypofluorescent areas (arrows).

perimetry confirmed the presence of these scotomata. Retinal function studies were otherwise normal.

The fluorescein angiographic findings are unlike those seen with acute disorders of the choriocapillaris or retinal pigment epithelium, such as acute posterior multifocal placoid pigment epitheliopathy[3] or acute retinal pigment epitheliitis. Definite but subtle findings of hypofluorescence probably represent a blockage of the underlying choroidal fluorescence by the visible lesions located at the level of the deep sensory retina. We are not certain whether the small intraretinal hemorrhage observed in the left eye was a coincidental finding or indicative of small vessel disease. Bos and Deutman[1] reported somewhat dilated perimacular capillaries in two of their cases. It is not certain that an abnormality of the retinal capillaries is of significance in this disorder.

The retinal lesions were best seen by using red-free light and contact lens biomicroscopy. We believe the deep sensory retina, and specifically the photoreceptor cell layer, to be the principal site of involvement in this disease. Functional impairment as evidenced by dense paracentral scotomata is consistent with the interpretation that the photoreceptor cell layer is of pathophysiologic significance. Contact lens biomicroscopy demonstrating the defects to be at the level of the sensory retina also supports this supposition.

All previously reported cases[1,2] have been associated with a recent infectious process. Our case further supports this observation. Bos and Deutman[1] reported six cases, five of which were in females, and of these, four were taking oral contraceptives. Additionally, the patient described by Rush[2] was also using oral contraceptives. However, our patient and the one male described by Bos and Deutman[1] make it difficult to implicate sex predilection or oral contraceptives with acute macular neuroretinopathy.

SUMMARY

A 17-year-old boy had minor visual impairment, paracentral scotomata, and parafoveal retinal lesions following a presumed viral infection. Contact lens biomicroscopy demonstrated the retinal de-

fects to be located at the level of the deep sensory retina. Fluorescein angiography revealed subtle areas of hypofluorescence which corresponded to the visible disturbances of the sensory retina. Follow-up examination three months later revealed persistent complaints of paracentral scotomata and persistent, but less recognizable retinal lesions. We believe the primary site of involvement to be the deep sensory retina.

References

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Ophthalmic miniature

The little children were in a pitiable condition—they all had sore eyes, and were otherwise afflicted in various ways. They say that hardly a native child in all the East is free from sore eyes, and that thousands of them go blind of one eye or both every year. I think this must be so, for I see plenty of blind people every day, and I do not remember seeing any children that hadn't sore eyes. And, would you suppose that an American mother could sit for an hour, with her child in her arms, and let a hundred flies roost upon its eyes all that time undisturbed? I see that every day. It makes my flesh creep. Yesterday we met a woman riding on a little jackass, and she had a little child in her arms; honestly, I thought the child had goggles on as we approached, and I wondered how its mother could afford so much style. But when we drew near, we saw that the goggles were nothing but a camp-meeting of flies assembled around each of the child's eyes, and at the same time there was a detachment prospecting its nose. The flies were happy, the child was contented, and so the mother did not interfere.

Mark Twain, *Innocents Abroad*
New York, Harper and Harper, 1911

BARE SCLERA CLOSURE IN RETINAL DETACHMENT SURGERY

MICHAEL E. BARRICKS, M.D., AND GEORGE F. HILTON, M.D.

San Francisco, California

Limbal peritomy has been used in retinal detachment surgery for many years. In 1965, Jungschaffer[1] presented his technique of incision of the conjunctiva and Tenon's capsule at the corneoscleral limbus. In 1974, King and Schepens[2] described their technique and reported their results in 396 cases. We have modified this technique by recessing the conjunctiva approximately 3 mm posterior to the corneoscleral limbus as we close the limbal wound, with some advantages and no significant disadvantages.

MATERIAL AND METHODS

We used limbal peritomy in 600 consecutive cases from 1968 to 1975. The technique described herein was used in all cases in which the conjunctiva was opened 360 degrees. In some cases, in which a segmental buckle was used, the conjunctiva was only opened 140 to 180 degrees. If retinal surgery was done soon after cataract surgery, the incision through the conjunctiva was made 3 mm posterior to the corneoscleral limbus in the superior quadrants to avoid disturbing the recent cataract wound.

After routine preparation and draping, an eyelid speculum was inserted between the eyelids. The combined layer of conjunctiva and Tenon's capsule was grasped at the corneoscleral limbus with toothed forceps. An incision down to the sclera was made with Wescott scissors. The posterior blade of the scissors was then inserted through the incision and placed so that it lay flat on the sclera. The fused conjunctiva and Tenon's capsule were separated from the underlying sclera by sliding the posterior blade along the scleral surface. Conjunctiva and Tenon's capsule were then incised at the corneoscleral limbus by closing the blades of the scissors. In the same fashion, this incision was carried around the entire corneoscleral limbus separating the fused layers from the underlying sclera. Two relaxing incisions perpendicular to the corneoscleral limbus were made through conjunctiva and Tenon's capsule at the 3 and 9 o'clock meridians. The relaxing incisions were approximately 6 mm in length (Fig. 1). The nasal incision did not reach the plica semilunaris. When the limbal peritomy was completed, we opened each quadrant by grasping conjunctiva and Tenon's capsule and lifting these tissues away from the adjacent sclera. We then inserted scissors into each quadrant, slid the closed blades over the scleral surface, and then broke the episcleral-Tenon's ad-

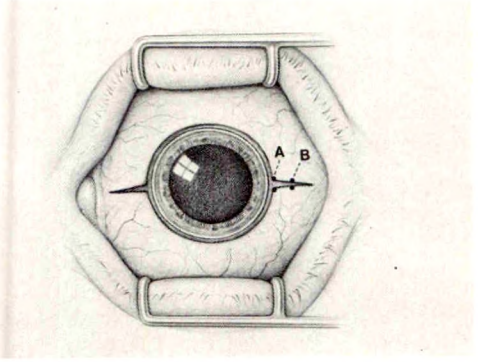


Fig. 1 (Barricks and Hilton). Limbal incision of the conjunctiva and Tenon's capsule with radial incisions at 3 and 9 o'clock. Point A is at the corneoscleral limbus, and point B is 3 mm posterior.

From the Department of Ophthalmology, University of California Medical Center, San Francisco, California. This study was presented in part at the Retina Society Scientific Meeting, Los Angeles, California, Nov. 5, 1977.

Reprint requests to Michael E. Barricks, M.D., University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284.

hesions by opening the blades. At this point, excellent exposure was available to sling the muscles and proceed with scleral buckling.

To close the peritomy, we grasped the anterior margin of the conjunctiva and Tenon's capsule with two forceps and pulled it back to the original position. The four corners created by the radial relaxing incisions were then identified. A 5-0 plain catgut suture, with a scleral spatula needle, was passed through conjunctiva and Tenon's capsule approximately 3 mm posterior to one corner (Fig. 2). To bury the knot, we began the suture on the underside (scleral side) of Tenon's capsule. We then grasped the other margin of the relaxing incision and passed the needle through 3 mm posterior to the corner. The needle was then passed through the superficial sclera 3 mm posterior to the corneoscleral limbus while the globe was stablizied with a twist fixation hook. The suture was then tied and the knot buried. The process was repeated on the opposite side of the globe. Additional sutures were occasionally required to close the radial incisions if they gaped posteriorly. The margin of the conjunctiva was pushed posteriorly with a cotton-tipped applicator. The anterior tips of the four "corners" were excised (Fig. 2). An annular zone of bare sclera, approximately 3 mm wide, should be present around the corneoscleral limbus. If the conjunctiva or Tenon's capsule did not easily remain at least 3 mm posterior to the corneoscleral limbus, they were trimmed back with scissors. Tenon's capsule becomes white when irrigated with saline and is easily identified. If redundant Tenon's capsule prolapsed anteriorly from beneath the conjunctiva, we grasped it with forceps, pulled it forward, and trimmed it with scissors. It retracted, leaving a smooth conjunctival margin well posterior to the corneoscleral limbus.

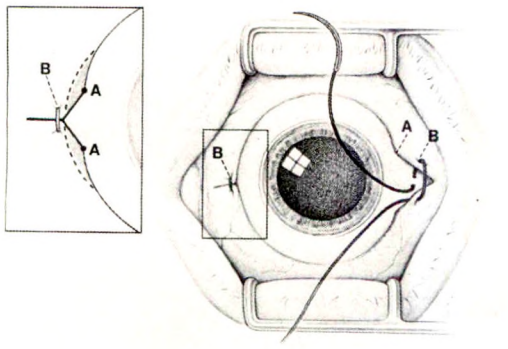


Fig. 2 (Barricks and Hilton). Bare sclera closure with recession of the conjunctiva, secured by two sutures with buried knots at points B. Inset, Excision of redundant triangles of conjunctiva at points A (shaded areas).

Results

The cosmetic results were generally good. The eyes often appeared white within two weeks. We noted no symblepharon, chronically irritated eyes, or blind fistulas lined with conjunctiva. There was no shortening of the conjunctival fornices; rather the fornices were slightly deeper postoperatively. The problem of impaired ophthalmoscopy, because of chemosis over the cornea, was avoided.

No significant complications occurred. In a few eyes, prolapse of the conjunctiva between the eyelids occurred nasally during the early postoperative period. These prolapses were treated by reduction of the herniated tissues with a glass rod (the most convenient is a fever thermometer) and taping the eyelids tightly closed. Such prolapses were usually resolved in two to four days. In one case, an intermarginal eyelid suture was needed to secure the eyelids as the conjunctival swelling subsided.

Discussion

The advantages of limbal peritomy over the traditional posterior peritomy have been described by King and Schepens.[2]

With a limbal peritomy, the anatomic relationship between conjunctiva and Tenon's capsule is usually unaltered. The limbal peritomy is faster to perform because minimal suturing is required and the eye is more comfortable. In a posterior peritomy the anterior cuff of tissue may shrink or shred during the procedure, so that minimal tissue is left for suturing. Therefore, the posterior edge of the incision is advanced during the closure shortening the fornices. This complication is avoided in limbal peritomy. Limbal peritomy also eliminated overlapping of the anterior and posterior lips of the conjunctival wound. Such overlapping may lead to inclusion cysts or blind passages, which may cause an irritable eye. The line of closure is placed well anterior of the silicone implants.

The base sclera closure offered some advantages over the standard limbal peritomy closure. In the technique described by King and Schepens,[2] the sutures were placed near the corneoscleral limbus and tied with exposed knots. To prevent the conjunctiva from creeping over the cornea, they placed a suture anchoring the conjunctiva and Tenon's capsule just posterior to the corneoscleral limbus at the 12 o'clock position and sometimes at the 6 o'clock position. The bare sclera technique eliminates the need for the anchoring suture at the 12 o'clock position and leaves a clean white rim around the corneoscleral limbus. During the postoperative period, the eye is quiet in appearance and comfortable because there is no suture material adjacent to the corneoscleral limbus. Burying the suture knots also makes the eye less irritable. The annular zone of bare sclera is subsequently covered by a layer of remodeled conjunctiva, leaving a smooth, uninjected limbal area.

We have not encountered any disadvantages associated with the technique. The conjunctiva migrating over the bare sclera superiorly may be tightly adherent, making a later glaucoma filtering procedure difficult. Although it is more difficult, a trabeculectomy procedure can be done. We have had no problem with the incision for subsequent retinal operations or cataract extraction.

SUMMARY

Our modification of the limbal peritomy technique in retinal detachment surgery involved recession of the conjunctiva 3 mm posterior to the corneoscleral limbus as the conjunctiva was closed. This recession offered some advantages over the standard nonrecessed method: fewer sutures were required; postoperative ophthalmoscopy was not impaired by conjunctiva swelling over the cornea; the eye was comfortable and quiet in appearance because there was no suture material or inflamed conjunctiva adjacent to the corneoscleral limbus. We have not encountered any disadvantages in several hundred cases.

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A SIMPLIFIED SCLERAL REINFORCEMENT TECHNIQUE

FRANK B. THOMPSON, M.D.

Pasadena, California

In the past eight years I have operated on 52 eyes for myopic degeneration by using the simplified reinforcement technique. In ten cases, the operation was preceded or followed by cataract extraction, without complications. In two cases, reoperation was necessary because a scleral strip had been incorrectly placed during previous surgery. The follow-up time extended from one month to seven years.

MATERIAL AND METHODS

The type and size of scleral graft have been described previously.[1] I obtained two grafts from each donor eye by contouring the grafts posteriorly from the cornea on either side of the optic nerve in a curvilinear pattern. This procedure doubled the amount of material available, and took less time to perform.

Whole donor eyes were used because it was necessary to include the corneal tissue to obtain a sufficient length, as the myopic eyes requiring reinforcement needed all the donor tissue available. I attempted to use eyes from which the cornea or corneoscleral button had been removed, by taking a spiral graft from anterior to posterior. However, these grafts were difficult to place and keep flat against the globe, because they did not follow the normal contour of the eyeball.

Eye bank specimens that have been kept refrigerated under sterile conditions, but which are slightly too old for use as corneal grafting material, may be used. Since the scleral graft is only for reinforcement and does not depend on the viability of cellular structure, specimens can be seven to eight days old.

The specific details of placement were described previously,[1] but some changes have evolved (Fig. 1). No canthotomy is generally necessary even on Oriental eyes, which have much smaller palpebral fissures and tighter eyelids. However, if visibility of the strip posteriorly is a problem, a canthotomy should be performed because accurate placement of the strip is crucial.

Placement of the strip over the posterior pole was made easier by using an instrument I made by bending the tip of a flat iris repositor in a stair-step fashion, and then curving the instrument to fit the contour of the globe (Fig. 2). The cotton-tipped applicator used previously for placement would frequently pull the strip forward as it was withdrawn; the shaped tip of the new instrument held the strip in place.

In those cases where the muscle was divided into two strips, it was important that the strip be placed in back of both bundles of the inferior oblique muscle. The oblique tendon must not be split. When this occurs a reoperation is necessary.

The inferior oblique muscle was the key to the entire operation, because the insertion of this muscle held the strip over the macula without suturing. The dissection was done so as to avoid tearing of the vortex veins, both to prevent choroidal edema and hemorrhage and to facilitate surgery because an actively bleeding vortex vein is difficult to control and makes posterior visibility extremely difficult.

When the strip was in position and the inferior oblique muscle was released from its traction suture, an anectine drip

From the Department of Ophthalmology, University of Southern California School of Medicine, Los Angeles, California.

Reprint requests to Frank B. Thompson, M.D., 206 E. Los Tunas Ave., San Gabriel, CA 91776.

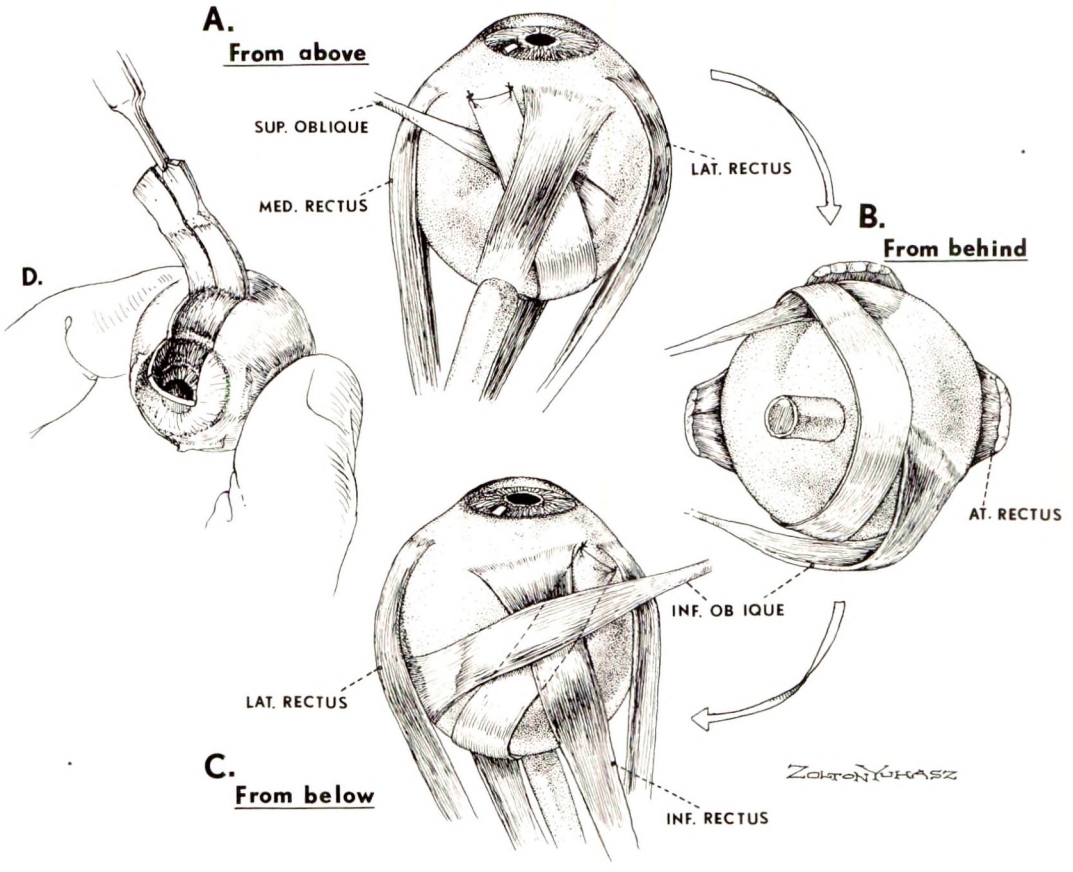


Fig. 1 (Thompson). Placement of a scleral homograft in the right eye. A, View from above showing graft placement nasal to the superior oblique muscle insertion. B, Posterior view showing graft held over macular area by insertion of inferior oblique muscle. C, View from below showing insertion of strip nasal to inferior rectus muscle insertion. D, Donor eye showing scleral grafts being dissected and including corneal tissue to obtain sufficient length.

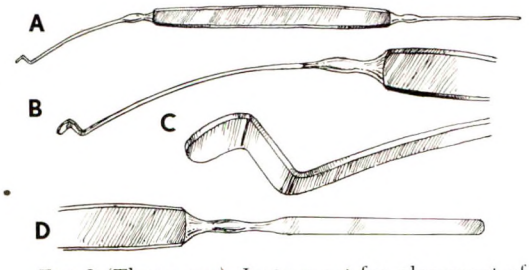


Fig. 2 (Thompson). Instrument for placement of strip over posterior pole. A, View showing curves of repositor to fit the contour of the globe. B, Larger view showing stair-step bend in tip. C, Magnified view of the tip. D, View of the opposite uncurved end of iris repositor.

was started on the patient to contract the extraocular muscles and pull the strip in place.

Instead of the 4-0 polyester fiber sutures used to fix the strip superiorly and inferiorly, 5-0 chromic collagen sutures were used. The polyester sutures remained indefinitely, but occasionally, they extruded or caused postoperative inflammation. By the time the collagen sutures were absorbed, the strip was firmly fixed to the underlying sclera. It was not necessary to dissect a scleral bed for the strip.

If further ocular surgery was anticipated, then minor modifications in the technique were necessary. In many cases, scleral reinforcement has been performed on patients with fairly dense cataracts. As long as the posterior pole and periphery of the retina were apparent with the indirect ophthalmoscope, the scleral reinforcement was done first, followed by the cataract surgery, because the loss of visual acuity from macular deterioration was usually permanent and irreversible, whereas the loss of vision from the cataract was reversible. The myopia surgery, therefore, takes precedence. When cataract surgery was anticipated after scleral reinforcement, the superior conjunctival incision was placed as posterior as possible (4 to 5 mm) so as not to disturb the limbal area if a limbal-based flap was used in the cataract technique.

Because the routine detachment of extraocular muscles for visualization of the posterior portion of the globe is not necessary, anterior segment necrosis is not a complication. In the occasional case where muscle surgery is needed for a preoperative strabismus, the muscle surgery can be done at the same time as scleral reinforcement as long as two adjacent muscles are not operated on. Resection-recession of medial and lateral rectus muscles have been successful. Surgery on the inferior oblique muscle is not desirable, however, because this muscle keeps the strip in place.

In many cases cryosurgery to areas of peripheral degeneration after placement of the strip is beneficial because small open operculated retinal breaks have been detected and treated during the surgery, which were not visible on the preoperative examination (either because of poor patient cooperation, especially in younger patients, or poor visibility, or both). We believe this maneuver may have prevented retinal detachments in our cases.

Results

The ultimate value of the procedure can be finally evaluated only after careful clinical comparison of a large number of patients, treated and untreated, over a long follow-up period (20 to 40 years). The first patients in this study have been observed from five to seven years (Table). For those not lost to follow-up, the vision in almost all cases has remained at the level at which surgery was performed, or it has improved. In one case (Case 6) the patient suffered a macular hemorrhage two years after surgery similar to the hemorrhage seen in high myopia. The patient was treated with argon laser, and the condition stabilized. This patient had no increase in staphyloma.

In some cases eyes were operated on at a lower level of myopia than the guideline indicates. These patients, however, showed posterior staphyloma, severe macular deterioration, or fluorescein angiography changes compatible with a higher degree of myopia. These changes were sometimes inexplicably seen at lower levels of myopia than were expected.

Discussion

Since the original description by Borley and Snyder[2,3] of the use of a scleral homograft to preserve vision, and the subsequent report by Borley and Miller,[4] the popularity of the procedure seems to have waned in the United States. It is, however, being performed by an increasing number of surgeons outside of the United States. Bulyaev and Ilyina[5] used both fascial (eight cases) and scleral homografts in 102 cases, with good results. Fydorov (personal communication, June 1977) used our technique[1] in 150 cases, obtaining a 98.1% effectiveness with no serious complications.

Reasons for the unpopularity of this procedure in the United States may be (1) the difficulty in selecting patients who

TABLE

RESULTS OF SCLERAL REINFORCEMENT SURGERY ON 52 EYES*

Patient No., Sex, Age (yrs)	Date of Surgery	Visual Acuity		Myopia		Follow-up (mos)	Pertinent Information
		Pre-operative	Post-operative	Pre-operative	Post-operative		
1, M, 47	6/26/70	6/60 (20/200)	6/12 (20/40)	−11.00	−11.00	84	Patient had bilateral cataract
	11/4/70	6/12 (20/40)	6/9 (20/30)	−10.50	−11.00	80	Cataract surgery in 1976 (+2.75) (+3.00)
2, M, 8	12/15/70	6/18 (20/60)	6/12 (20/40)	−21.50	−21.00	7	None
	4/2/71	6/9 (20/30)	6/12 (20/40)	−21.00	−21.00	3	None
3, F, 21	11/1/71	CF 7 ft.	6/6 (20/20)	−9.75	−12.50	66	Laser to L.E. 1973 (retinal tear)
	12/17/71	6/12 (20/40)	6/6 (20/20)	−9.00	−10.00	60	None
4, M, 55	12/6/72	6/9 (20/30)	6/12 (20/40)	−12.50	No recent refraction	54	None
	3/16/73	6/9 (20/30)	6/12 (20/40)	−11.00	No recent refraction	51	None
5, M, 63	1/21/72	6/7.5 (20/25)	6/7.5 (20/25)	−7.00	−6.75	64	None
	1/12/73	6/45 (20/150)	6/30 (20/100)	−5.75	−5.50	52	None
6, F, 40	2/18/72	6/15 (20/50)	6/60 (20/200)	−17.00	−16.00	60	Retinal edema and hemorrhages in 1974 treated with argon laser
	4/11/73	6/15 (20/50)	6/9 (20/30)	−13.00	−12.00	48	None
7, M, 50	3/3/72	6/7.5 (20/25)	6/7.5 (20/25)	−11.25	No record	62	None
8, M, 33	12/11/74	6/24 (20/80)	6/15 (20/50)	−17.50	−17.50	38	Surgery done elsewhere
	2/6/74	6/24 (20/80)	6/21 (20/70)	−21.50	−16.50	36	Developed postoperative choroidal hemorrhage

(*Table continued on next page.*)

TABLE (*continued*)

RESULTS OF SCLERAL REINFORCEMENT SURGERY ON 52 EYES*

Patient No., Sex, Age (yrs)	Date of Surgery	Visual Acuity		Myopia		Follow-up (mos)	Pertinent Information
		Pre-operative	Post-operative	Pre-operative	Post-operative		
9, M, 10	1/22/75	6/15 (20/50)	6/12 (20/40)	−9.00	−8.75	10	None
10, F, 60	5/21/75	6/60 (20/200)	6/21 (20/70)	−20.00	Would be A+ due to aphakia	24	Cataract surgery 1976
	8/6/75	6/18 (20/60)	6/12 (20/40)	−20.00	Would be A+ due to aphakia	21	Cataract surgery 1975
11, F, 60	6/17/75	6/60 (20/200)	6/7.5 (20/25)	−11.00	+ 3.00 due to cataracts	22	Cataract surgery 2/19/76
	8/27/75	6/21 (20/70)	6/18 (20/60)	−10.75	+ 2.75 due to cataracts	20	Cataract surgery 3/1/76
12, F, 8	7/10/75	6/9 (20/30)	6/12 (20/40)	−8.00	−8.00	19	None
	12/18/75	6/9 (20/30)	6/6 (20/20)	−8.75	−9.00	14	None
13, M, 73	12/3/75	6/15 (20/50)	6/12 (20/40)	−7.25	With another physician	15	PSC cataract R.E.
14, F, 63	1/7/76	6/9 (20/30)	6/7.5 (20/25)	With another physician	With another physician	15	None
15, F, 61	2/4/76	6/15 (20/50)	6/24 (20/80)	−12.75	Not checked since surgery	15	Cataract surgery 4/26/77
16, M, 5	5/4/76	6/120 (20/400)	6/60 (20/200)	−14.00	−12.50	12	None
17, F, 31	8/18/72	6/18 (20/60)	6/9 (20/30)	−14.50	−15.50	57	PSC cataracts both eyes
	1/26/73	6/12 (20/40)	6/15 (20/50)	−16.50	−15.50	52	None

TABLE (*continued*)

RESULTS OF SCLERAL REINFORCEMENT SURGERY ON 52 EYES*

Patient No., Sex, Age (yrs)	Date of Surgery	Pre-operative	Post-operative	Pre-operative	Post-operative	Follow-up (mos)	Pertinent Information
18, F , 12	2/2/73	6/18 (20/60)	6/15 (20/50)	−11.00	−11.00	51	None
	7/20/73	6/9 (20/30)	6/15 (20/50)	−12.75	−11.50	46	None
19, M, 21	4/20/73	6/18 (20/60)	6/9 (20/30)	−16.00	−15.50	25	None
	9/26/73	6/18 (20/60)	6/9 (20/30)	−15.25	−15.00	20	None
20, F , 13	6/13/73	6/18 (20/60)	6/15 (20/50)	−15.00	−15.00	23	None
	7/19/73	6/15 (20/50)	6/12 (20/40)	−12.25	−12.50	22	None
21, M, 7	7/19/73	6/18 (20/60)	6/9 (20/30)	−8.75	−10.50	40	None
	12/2/73	6/18 (20/60)	6/9 (20/30)	−7.50	−7.75	45	None
22, F , 28	1/15/74	6/9 (20/30)	6/7.5 (20/25)	−10.25	−10.50	28	None
23, M, 13	4/3/74	6/60 (20/200)	6/45 (20/150)	−11.25	No refraction since surgery	4	None
24, F , 18	6/19/74	6/18 (20/60)	6/12 (20/40)	−12.50	−12.25	32	None
25, F , 75	6/8/76	6/12 (20/40)	6/12 (20/40)	Would be A+ due to aphakia		10	Cataract surgery before scleral surgery

(*Table continued on next page.*)

TABLE (*continued*)

RESULTS OF SCLERAL REINFORCEMENT SURGERY ON 52 EYES*

Patient No., Sex, Age (yrs)	Date of Surgery	Visual Acuity		Myopia		Follow-up (mos)	Pertinent Information
		Pre-operative	Post-operative	Pre-operative	Post-operative		
26, F, 54	11/1/72	6/60 (20/200)	6/7.5 (20/25)	−7.50		17	Cataract surgery 4/13/73
27, M, 38	6/30/76	6/21 (20/70)	6/15 (20/50)	−12.00		7	None
	11/2/76	6/7.5 (20/25)	6/7.5 (20/25)	−11.00		2	None
28, F, 44	8/12/76	6/15 (20/50)	6/9 (20/30)	−25.00	No refraction	6	None
	8/17/76	6/21 (20/70)	6/9 (20/30)	−20.00	No refraction	6	None
29, F, 35	2/22/77	CF 6 ft	6/120 (20/400)	−20.00	No refraction	3	PSC cataracts and preoperative esotropia
	4/19/77	6/45 20/150	6/45 20/150	−20.00	No refraction	1	PSC cataracts and preoperative esotropia
30, F, 72	5/3/77	6/60 (20/200)	6/30 (20/100)	Temporary glasses		1	
	6/22/77	6/60 (20/200)	6/21 (20/70)	−12.50	Temporary glasses		Cataract surgery 1977 Now aphakic
31, M, 34	6/15/77	6/18 (20/60)	6/18 (20/60)	−15.50	−15.50	3	None
32, F, 75	8/31/77	6/60 (20/200)	6/60 (20/200)	−13.00		1	Dense PSC cataract
33, M, 44	9/13/77	6/12 (20/40)	6/9 (20/30)	−18.25			None

*PSC designates posterior subcapsular cataract.

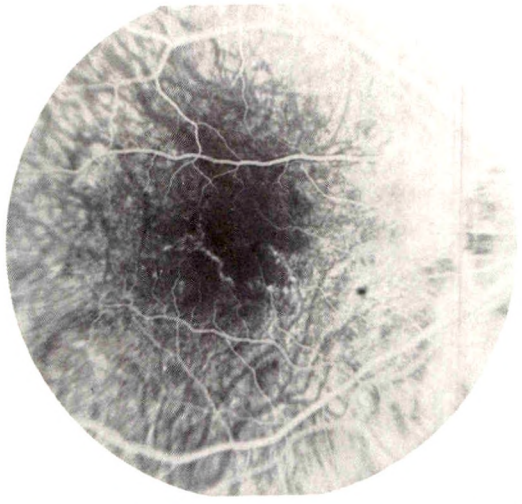


Fig. 3 (Thompson). Fluorescein angiogram of the eye illustrating a severe posterior staphyloma and deterioration of choroid and retina (too late for scleral reinforcement).

require surgery; (2) concern over serious complications; and (3) a general misunderstanding of the objective of the surgery.

Patient selection—Since most nearsighted patients stop progressing at the −5.00 to −7.00 diopter range and do not progress into the range of high myopia (−9.00 or greater) or malignant myopia, most myopic patients do not require surgery. In degenerative myopia there is deterioration of the connective tissue of the globe with fewer and thinner scleral fibers. The end result of the process is severe posterior staphyloma with choroidal and retinal deterioration (Fig. 3).

The patient for whom surgery is most necessary is the individual over 20 years of age, in whom (1) the myopia is greater than −10.00 diopters and the vision is decreasing (Fig. 4, left); (2) a posterior staphyloma is present; and (3) the macula is undergoing degenerative changes observed either directly or by fluorescein angiography (Fig. 4, right). In the patient 55 to 60 years of age or older, the degree of myopia does not usually increase rapidly. However, there is frequently a marked deterioration of the retina and choroid over the staphyloma, which is probably secondary to the more pronounced vascular changes in this age group. Surgery may also be indicated for the younger patient under 20 years of age with (1) myopia greater than −12.00 to −13.00 and a yearly increase in the myopia of greater than −2.00 diopters

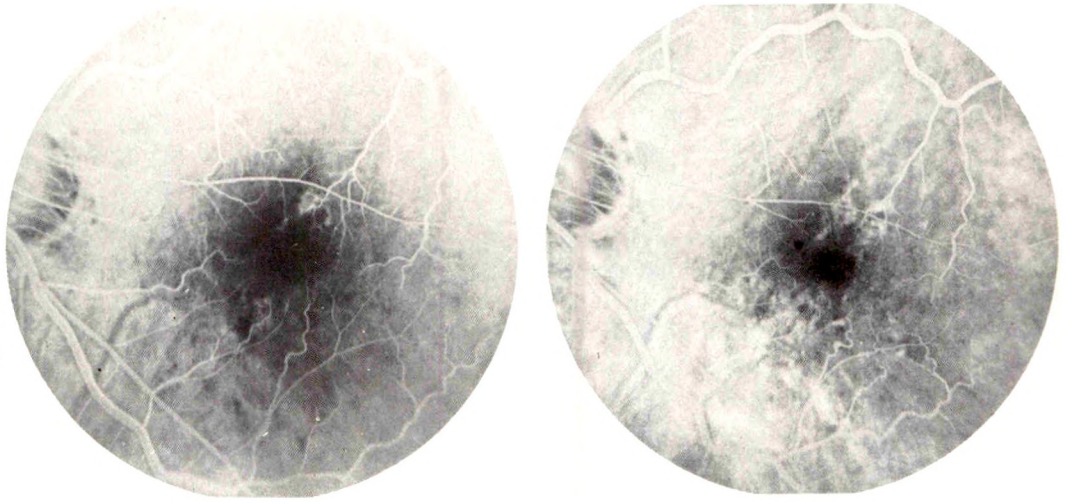


Fig. 4 (Thompson). Left, Fluorescein angiogram of deterioration around macula taken two months prior to scleral reinforcement. Right, Fluorescein angiogram taken five years after operation showing little change in macular deterioration and maintenance of good visual acuity.

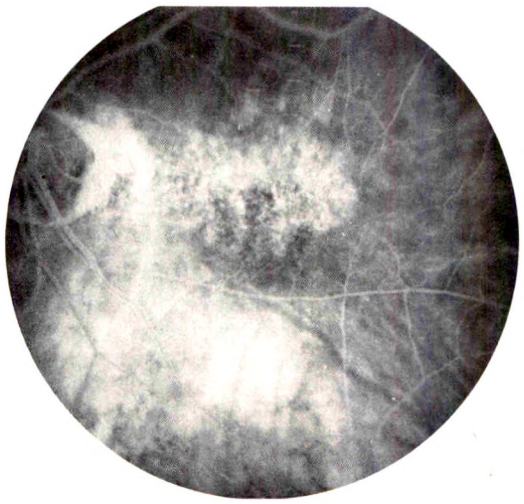


Fig. 5 (Thompson). Fluorescein angiogram taken four years after operation revealing no increase in the previously noted loss of pigment epithelium and lacquer cracks in macula with maintenance of improved vision.

(Fig. 5); (2) a posterior staphyloma; and (3) even if the present vision is good, with no observable fluorescein changes (this contradicts previous reports in which surgery was believed not to be indicated until demonstrable changes in vision had occurred). The objective of the surgery, however, is to prevent further visual loss (without necessarily improving present vision).

Serious complications—In the present study, and in the cases reported by Fydorov and Bulyaev and Ilyvina,[5] the incidents of serious complications have been near zero. There have been cases of severe conjunctival edema, transient muscle imbalance, subconjunctival hemorrhages, and the like, but no complication effecting visual acuity or ocular function.

Permanent muscle imbalance can be produced by the malposition of the strip, as was the case in one patient in whom the strip was incorrectly positioned in relation to the inferior oblique muscle, necessitating a reoperation. Additionally, the stripping of the muscles of their check ligaments and attachments to Tenon's capsule must be meticulously carried out to prevent later scarring.

Surgical objectives—Many patients and surgeons still view the scleral reinforcement as a method of decreasing the degree of myopia. The objective of the procedure is to strengthen the sclera over the posterior pole to prevent further staphylomatous changes, and increase the circulation by stopping the progressive thinning of the choroid.

Although visual improvement may be dramatic in some cases (as from counting fingers to 6/6 (20/20) in patient No. 3), the thrust of surgery is toward stopping the degenerative process, rather than reversing it (Fig. 5). One can, therefore, realistically expect only to stop the process at the point at which surgery is performed, thus making early surgery in younger patients more desirable.

Summary

A simplified scleral reinforcement technique performed on 52 eyes with myopic degeneration prevented further visual loss by strengthening of the sclera over the posterior pole. This scleral homograft was useful not only in older patients with high myopia and posterior staphyloma, but also in younger patients in whom the degenerative process could be stopped at an earlier stage. In all cases in which follow-up was possible, the visual acuity remained at the preoperative level before surgery was performed or it improved.

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JUXTAPAPILLARY RETINOCHOROIDITIS WITH A PSYCHIATRIC DISORDER POSSIBLY CAUSED BY *TOXOPLASMA*

YUKIO UCHIDA, M.D., YAYOI KAKEHASHI, M.D., AND KAZUKO KAMEYAMA, M.D.

Tokyo, Japan

Juxtapapillary retinochoroiditis[1] is characterized by a focal exudative lesion adjacent to the optic disk, and a fan-shaped defect in visual field which extends from the blind spot toward the periphery. Tuberculosis has been considered to be a frequent cause of this condition. Many juxtapapillary lesions are attributable to toxoplasmosis.[2] In addition to ocular tissues, the central nervous system is often involved in toxoplasmosis, and many kinds of neurologic manifestations may occur.

The diagnosis of ocular toxoplasmosis is usually made by the clinical picture of the fundus and by serological methods, such as hemagglutination test or the dye test. However, demonstration of the organism *Toxoplasma gondii* has rarely been possible.

CASE REPORT

A 32-year-old man was first seen at our clinic on Dec. 25, 1975, complaining of eye fatigue after reading, and floating spots before the right eye. At the beginning of August 1975, he complained of insomnia, loss of appetite, and headache. In November 1975, he developed psychiatric symptoms such as emotional excitement, hallucination, and delusion. He was hospitalized in the Department of Psychiatry, where the diagnosis of the manic phase of a manic-depressive psychosis was made. He had been healthy except for some tropical diseases such as malaria and yellow fever suffered in childhood.

Visual acuity was 6/5 (20/16) × +0.75 diopters in the right eye, and 6/5 (20/16) × +1.0 diopters in the left eye. Accommodative amplitude was 2.5 diopters in each eye. This lower value for his age apparently was caused by some medications administered for his psychiatric condition. The eyes showed no hyperemia, the corneas were clear, and the pupils reacted normally. The anterior chamber was clear in each eye. The positive results were limited to the right ocular fundus where the margins of the optic disk were blurred. Adjacent to the upper nasal aspect of the disk, an atrophic lesion with heavy pigmentation was evident. A slightly prominent white exudative lesion with fluffy edges, about 1.5 disk diameter in size, was seen on the lower side of the optic disk. The retinal vessels were partly covered by the lesion in which chalky white patches were noted. Fine floaters were observed in the vitreous. Perimetry showed a sector field defect extending from the blind spot to the upper periphery. The diagnosis of juxtapapillary retinochoroiditis was made on the basis of these findings. He was slightly febrile (37.4°C). The skull x-ray showed no calcifications. Neurologically, no abnormal reflex was noticed. Serum Wassermann reaction was negative. Urinalysis was normal. Blood tests gave the following results: hemoglobin 12.3g/dl, hematocrit 38%, red blood cell count 433 × 10^4, white blood cell count 9,700 mm^3 with polymorphonucleocytes 33%, lymphocytes 58.5%, eosinophils 5%, and monocytes 3.5%.

On Jan. 16, 1976, the focal exudative lesion was slightly enlarged and was accompanied by a small hemorrhage (Fig. 1). Visual acuity of the right eye decreased to 6/7.5 (20/25). The serum hemagglutination titer for *Toxoplasma* was in excess of 1:8, 192, and after re-examination it was 1:524,288. Dye test titer was 1:256. Some cerebrospinal fluid was aspirated; it was clear in appearance, and negative for



Fig. 1 (Uchida, Kakehashi, and Kameyama). Fundus photograph showing a focal exudative, and an atrophic lesion near the optic disk.

From the Department of Ophthalmology, Tokyo Women's Medical College, Tokyo, Japan.

Reprint requests to Yukio Uchida, M.D., Department of Ophthalmology, Tokyo Women's Medical College, 10 Kawada-cho Shinjuku-ku, Tokyo 162, Japan.

Nonne-Appelt and Pandy reactions. The fluid was injected into mice intraperitoneally. The patient received 1,200 mg of acetylspiramycin daily. On Jan. 29, 1976, visual acuity decreased to 6/10 (20/33), and the patient complained of more floaters and blurred vision.

On Feb. 2, 1976, visual acuity improved to 6/5 (20/16). The exudative lesion began to flatten, and the hemorrhage disappeared. One of the mice inoculated with the cerebrospinal fluid showed elliptic bodies in brain preparations which had the morphologic characteristics of a *Toxoplasma* cyst (Fig. 2).

On Feb. 26, 1976, floaters in the vitreous diminished markedly. The exudative lesion was obviously absorbed (Fig. 3), but the sector field defect remained unchanged. The psychiatric symptoms and ocular complaints had completely disappeared. The left eye remained normal.

Discussion

This patient came from West Africa where toxoplasmosis is prevalent as one of the endemic tropical diseases. Perkins[3] stated that most of his patients with ocular toxoplasmosis in England were found mainly among the people from that area.

Occurrence of a new focal exudative lesion adjacent to an old atrophic lesion in the fundus is considered as the characteristic mode of recurrent retinal toxoplasmosis. This phenomenon is caused by reactivated growth of *T. gondii*, which has long been dormant in the cyst. This patient had an old atrophic lesion with pigmentation adjacent to the optic disk.

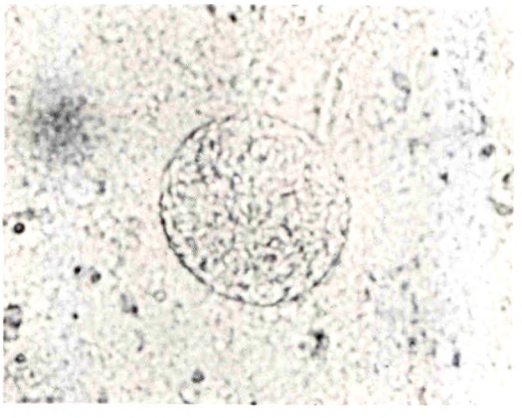


Fig. 3 (Uchida, Kakehashi, and Kameyama). The same fundus as shown in figure 1, but six weeks later. The exudative lesion is almost absorbed.

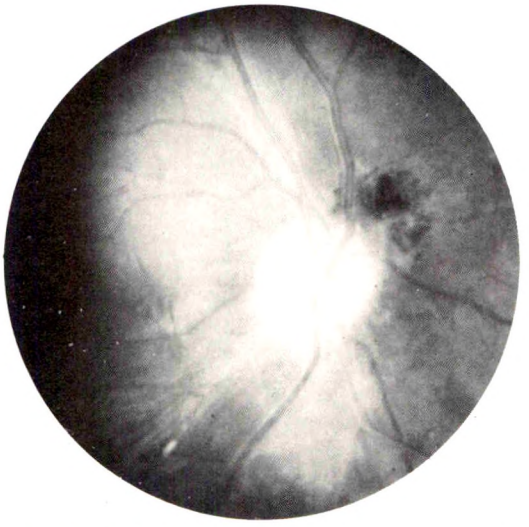


Fig. 2 (Uchida, Kakehashi, and Kameyama). Microphotograph of a *toxoplasma* cyst in brain preparation of a mouse inoculated with cerebrospinal fluid (fresh preparation, ×710).

The focal exudative lesion with the sector field defect had the typical clinical features of juxtapapillary retinochoroiditis. Additionally, high titers of hemagglutination antibodies and dye test antibodies as well as isolation of *T. gondii* from the cerebrospinal fluid, strongly suggest the toxoplasmic origin of this retinochoroiditis. The patient could not recall any episode of visual disturbance. Therefore, we think his condition is a recurrence of congenital toxoplasmosis.

Berengo and Frezotti[4] reported cases with active neuro-ophthalmic toxoplasmosis, and showed the importance of the association between central nervous system toxoplasmosis and ocular toxoplasmosis. Of their 19 cases, 12 had meningo-encephalitis. Severe, often fatal, toxoplasmosis of the nervous system has been described by several authors:[5–8] Except for an occasional slight increase in body temperature, there were no signs of meningo-encephalitis in our patient. Whether the psychiatric signs observed in our patient were incidental or secondary to central nervous system toxoplasmosis,

is not certain. Neurologic disorders are often associated with psychiatric symptoms; conversely, any type of psychiatric disturbance may occur in neurologic disease. Isolation of the organism from the cerebrospinal fluid showed involvement of our patient's central nervous system by *Toxoplasma*. Acetyl spiramycin had a favorable effect on the ocular condition, and the exudative lesion was absorbed within six weeks. During this period, the patient's psychiatric disorder improved simultaneously with improvement in retinochoroiditis. Therefore, the possibility that the psychiatric condition was caused by *Toxoplasma* cannot be excluded.

SUMMARY

A 32-year-old man suffered from juxtapapillary retinochoroiditis in the right eye and a psychiatric disorder. The diagnosis of toxoplasmosis was supported by the clinical ocular findings, serologic examinations, and isolation of the organism from the cerebrospinal fluid. As the retinochoroidal lesion absorbed, the psychiatric symptoms also disappeared during the course of six weeks.

ACKNOWLEDGMENT

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RETINAL ANEURYSMS IN ADULT CYTOMEGALOVIRUS RETINITIS

JAMES J. AUGSBURGER, M.D., AND RICHARD Y. HENRY, M.D.

Cincinnati, Ohio

Adult cytomegalovirus disease with ocular involvement was first described in 1959.[1] Several patients with necrotizing retinitis due to cytomegalovirus have been described since then. These individuals have been immunosuppressed and most have been renal homograft recipients.[2] Clinical features of the acute stage include patchy perivascular sheathing, narrowing of arteries and venules, scattered focal white lesions bordering well-demarcated zones of gray-white retinal necrosis, and associated retinal hemorrhages.[2–11] Vitreous haze, vitreous hemorrhage,[5] and exudative[2,5] and rhegmatogenous[10] retinal detachments have been reported in severe cases. Pathologic features include the presence of cytomegalovirus inclusions within the retina, pigment epithelium, and vascular endothelial cells in affected nonnecrotic zones as well as coagulative necrosis of the severely affected tissues.[2,3,6] Perivascular inflammatory cell infiltration is often evident.[2,3,6]

We describe herein arterial, capillary, and venous aneurysms in the retina of a patient with cytomegalovirus infection.

CASE REPORT

A 7-year-old boy had chronic renal failure in 1966. Family history was noncontributory for renal disease. Renal biopsies showed bilateral hypoplastic kidneys. Renal function gradually deteriorated during the next three years. The patient was hypertensive and anemic in August 1969. Blood pressures averaged 145/120; however, he did not have fundus features of hypertensive retinopathy during this period of systemic hypertension. Blood pressures were controlled at an average of 135/90 on reserpine. Hematologic evaluation confirmed the diagnosis of microcytic anemia of renal failure. Peritoneal dialysis was begun in September 1969. The patient underwent a cadaveric renal homotransplantation with bilateral nephrectomy in late October 1969. Pathologic examination of his kidneys confirmed the diagnosis of bilateral hypoplastic kidney, and also demonstrated superimposed chronic pyelonephritis. Since the renal transplantation, the patient has remained normotensive without antihypertensive medication.

Primary graft rejection led to a repeat renal transplantation in 1971. Shortly thereafter, a blood culture was positive for cytomegalovirus and the cytomegalovirus complement fixation titer rose from 1:2 to 1:8. A second graft rejection led to a third renal transplantation in 1976. The patient reported blurred vision in the right eye and was examined in the Cincinnati Children's Hospital Eye Clinic in July 1977, at age 18 years. Visual acuity was R.E.: 6/180 (20/600) and L.E.: 6/6 (20/20). Pupillary reactions to light were normal; no afferent pupillary defect was detected. The patient had a small, central, posterior subcapsular cataract in each eye. The right retina showed fluffy whitening in the papillomacular bundle. Retinal hemorrhages, many of which were flame-shaped, overlay the opaque white area. Several vessels in the papillomacular bundle were partially obscured, and the left fundus was normal. No hypertensive retinal changes were detected and the patient was normotensive at this time. No changing cardiac signs suggestive of subacute bacterial endocarditis were evident. We made the incorrect diagnosis of a branch vascular occlusion.

Fluorescein angiography of the right fundus showed blockage of choroidal fluorescence in the affected papillomacular area. Specific retinal vessel fluorescence was partially obscured in this region, but several small, fusiform dilations of the arterioles were evident. Leakage of fluorescein into the affected retina gradually obscured the vascular pattern. The vascular pattern of the uninvolved retina was normal (Fig. 1).

On follow-up examination six weeks later, a similar process was noted in the extramacular retina of the left eye. Visual acuity remained L.E.: 6/6 (20/20) and the patient was asymptomatic for this eye. Fluffy retinal whitening was present above the disk and extended superiorly and temporally (Fig. 2). Several similar satellite foci surrounded this zone. Extensive retinal hemorrhages covered some of the whitened retina, retinal arterioles in the affected area were narrow, and the vascular pattern in the unaffected areas was normal. We suspected cytomegalovirus retinitis at this time.

Fluorescein angiography of the left fundus showed multiple fusiform aneurysmal beads along several branch retinal arteries and arterioles, capillaries, and venules in the affected area (Fig. 3). A coarsened capillary network and numerous capillary

From the Department of Ophthalmology, University of Cincinnati Medical Center, Cincinnati, Ohio.

Reprint requests to James J. Augsburger, M.D., Department of Ophthalmology, Room 6004, Medical Science Building, University of Cincinnati Medical Center, Cincinnati, OH 45267.



Fig. 1 (Augsburger and Henry). Right eye. Fluorescein angiogram shows papillomacular fluorescence blockage and vascular leakage. The entire retinal vascular pattern apart from the papillomacular bundle is normal.

microaneurysms were evident. The white retinal area was so opaque that it blocked choroidal fluorescence. Leakage of fluorescein into the presumably necrotic retina gradually obscured the specific vascular fluorescence. Cultures of blood and urine were

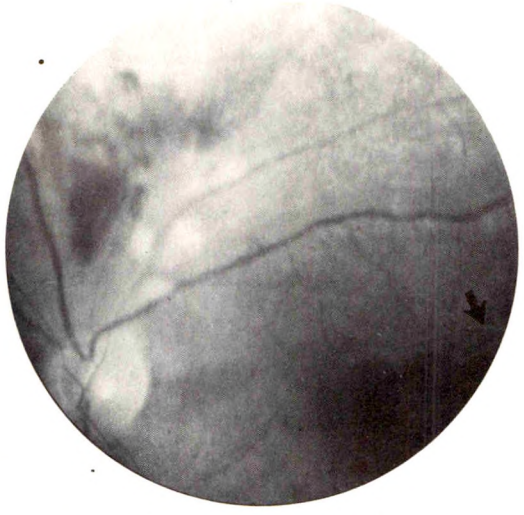


Fig. 2 (Augsburger and Henry). Left eye. Fundus shows fluffy retinal whitening and associated retinal hemorrhages extending superiorly and temporally from the disk. The arteries appear narrowed; no aneurysms can be demonstrated. The white branching figure (arrow) is an artifact; this is not a vascular structure.

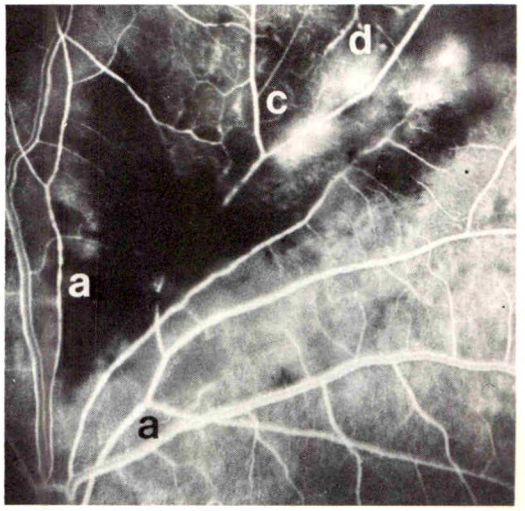


Fig. 3 (Augsburger and Henry). Left eye. Fluorescein angiogram shows fusiform aneurysmal beads along several branch retinal arteries and arterioles (a), coarsening of the capillary network (c), and small capillary and venular aneurysms (d).

positive for cytomegalovirus. Prednisone dosage was reduced, and the patient was given systemic cytosine arabinoside for 14 days; cultures of blood, urine, and saliva were negative for cytomegalovirus. The acute retinopathy spread peripherally to the oral zone superiorly and superotemporally. Retinal arterial and venous aneurysms were clinically evident in the advancing area of acute retinopathy; however, fundus photographs were not obtained at that time. The acute retinopathy slowly subsided, leaving widespread chorioretinal atrophy and pigmentation as well as white, attenuated arteries in the affected areas (Fig. 4). The aneurysmal changes disappeared as the atrophic changes developed.

The patient developed a rhegmatogenous retinal detachment in the left eye in March 1978. The principal retinal break was an irregular equatorial tear along the interface of the affected and unaffected areas superonasally. This detachment was successfully repaired.

Discussion

The incidence of cytomegalovirus retinitis following renal transplantation has been estimated to be in the range of 1.3%[7] to 4%,[9,12] or 5%,[4] usually occurring in individuals with chronic cytomegalovirus viremia.[12] Although the clinical picture in the acute stage is distinctive, if not pathognomonic, so few cases of cytomegalovirus retinitis have been diagnosed by

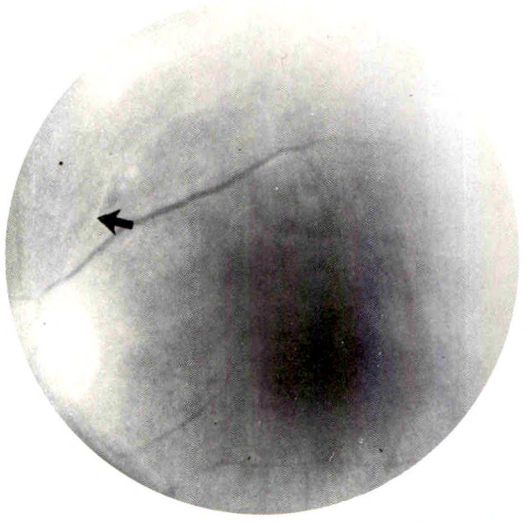


Fig. 4 (Augsburger and Henry). Left eye. Fundus shows the same area shown in Figures 2 and 3. In the atrophic stage the superotemporal artery is extremely attenuated and white (arrow), chorioretinal atrophy appears in the area extending superiorly and temporally from the disk, and the fluffy retinal whitening and retinal hemorrhages have largely resolved.

ophthalmologists outside large renal transplantation centers, that the hemorrhagic, necrotic retinopathy is often erroneously diagnosed as a retinal branch vein occlusion.[3] Progression of the retinitis in an immunosuppressed renal homograft recipient usually leads to the correct diagnosis.

Retinal aneurysms have not been previously described in cytomegalovirus retinitis. That such aneurysmal dilations should occur seems reasonable in view of the pathologically reported vascular endothelial involvement by cytomegalovirus.[3] Reported fluorescein angiographic features of acute cytomegalovirus retinitis include narrowing of the major retinal vessels and extensive leakage from the capillary bed in the regions of involvement.[5,7,8] The acute stage fluorescein fundus angiograms of our patient show arterial narrowing and profuse leakage from the capillaries in the affected regions. Coarsened retinal capillary networks in the involved areas suggest irregular perfusion. Arterial and arteriolar, capillary, and venular aneurysms in the affected areas are caused by damage to the vascular endothelial cells and the surrounding supportive cells.

Other causes of multiple retinal vascular aneurysms must be considered in this case. Systemic hypertension in a young person may produce a retinopathy characterized by retinal microaneurysms, flame-shaped retinal hemorrhages, cotton-wool patches, and generalized arterial attenuation. Although our patient was significantly hypertensive for several months before his initial renal transplantation in 1969, hypertensive retinopathy was not detected at that time. During the period of active cytomegalovirus retinitis, and consistently following the initial transplantation, the patient was normotensive without treatment. We do not believe systemic hypertension was a contributing factor in the development of the localized aneurysmal changes.

Diabetes mellitus retinopathy may include capillary microaneurysms and fusiform venous aneurysms, but our patient was not diabetic.

Periarteritis nodosa retinopathy may exhibit retinal vascular abnormalities similar to those of our patient. However, an extensive immunological and clinical evaluation failed to reveal any evidence which supports this diagnosis.

Leber's multiple miliary aneurysms of the retina may produce a fluorescein angiographic appearance similar to that found in our patient. However, it seems unlikely that the portions of the retinas that eventually became affected by cytomegalovirus retinitis would have been identical to those affected by Leber's aneurysms. Furthermore, the portions of the left fundus, which were subsequently involved by cytomegalovirus retinitis, were examined carefully at the time of acute involvement

of the right retina and were found to be normal.

SUMMARY

We observed aneurysms of the retinal arteries, capillaries, and venules occurring in a patient with cytomegalovirus retinitis. These aneurysms were caused by involvement of the retinal vascular endothelium resulting in focal weaknesses in the vascular walls. The clinical appearance of this retinitis superficially resembled retinal branch vein occlusion.

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CENTRAL RETINAL VASCULAR OCCLUSION ASSOCIATED WITH ORAL CONTRACEPTIVES

G. CLEVELAND STOWE III, M.D., Z. NICHOLAS ZAKOV, M.D., AND DANIEL M. ALBERT, M.D.

Boston, Massachusetts

The association between the use of oral contraceptives and systemic thromboembolic disease is well established.[1] Clinical reports of oral contraceptive-related retinal vascular occlusive conditions have also been published.[2–8] However, we are not aware of any histopathologic correlation of clinical retinal vascular disease to the use of oral contraceptives. We describe herein the pathologic findings associated with a combined central retinal vessel occlusion in a patient who had taken oral contraceptives for four years; no other apparent cause for occlusion was found.

CASE REPORT

A 40-year-old woman had progressive painless loss of vision in the left eye over a period of one week. She was otherwise asymptomatic, and denied any prodromal or concurrent ocular, neurologic, or systemic complaints. She was a gravida 7, para 6, aborta 1 woman who had taken Enovid-E (2.5 mg norethynodrel with 0.1 mg mestranol) for 21 months, and Ovral (0.5 mg norgestrel with 0.05 mg ethinyl estradiol) for 28 months. Her previous health was good, with no history of diabetes mellitus, hypertension, cardiac disorders, thromboembolic conditions, migraine headaches, ocular complaints, or trauma.

Physical examination revealed a normotensive patient free of any neurologic or cardiovascular findings. Visual acuity was 6/6 (20/20) in the right eye, and 6/240 (20/800) in the left eye. The ocular tension by applanation was normal. Ophthalmoscopic examination of the left fundus revealed diffuse flame-shaped retinal hemorrhages and dilated retinal veins consistent with central retinal vein occlusion. No abnormalities of the retinal arteries were noted. The right fundus was unremarkable and the remainder of the ophthalmic examination was within normal limits. An ocular examination seven months earlier was unremarkable, with visual acuity of 6/6 (20/20) in both eyes.

Systemic evaluation by her internist failed to reveal clinical evidence of thromboembolic conditions, cardiac disease, neurologic abnormalities, diabetes mellitus, or connective tissue disorders. The results of a complete blood cell count with differential, platelet count, sedimentation rate, urinalysis, chest x-ray film, and electrocardiogram were within normal limits.

At this time, the oral contraceptive was discontinued. Four months later she returned with acute ocular pain, intraocular pressure of 35 mm Hg by applanation and visual acuity of hand motions at 1 m in the left eye. A diagnosis of neovascular glaucoma was made and the patient's pain subsided after a retrobulbar alcohol injection. Medical treatment over the next 12 months failed to control the glaucoma; vision deteriorated to loss of light perception; persistent ocular pain developed and the left eye was enucleated. Except for the ocular findings, the patient had otherwise remained in good health. The results of all laboratory studies undertaken at the time of enucleation were within normal limits.

On follow-up examination she had an uneventful postenucleation course with an unremarkable ophthalmic examination one month later.

RESULTS

Gross—Examination of the enucleated left globe showed closure of the angle and iris pigment adhering to the anterior surface of the lens. The retinal vessels appeared white and the optic disk showed glaucomatous cupping.

Light microscopy—Serial sections of the optic nerve showed occlusion of both the central retinal artery and vein that was confirmed by Verhoeff's modified elastic stain (Fig. 1). The thrombotic lesions were characterized by a marked intimal proliferation with a myxomatous stroma and, in some sections, included the presence of giant cells of the Langhans' type (Fig. 2). We also noted a mild chronic inflammatory infiltrate involving the adventitia and walls of some, but not all, arteries and veins. The infiltrate was predominantly lymphocytic in nature with a

From the Howe Laboratory of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts.

Reprint requests to Daniel M. Albert, M.D., Howe Laboratory of Ophthalmology, 243 Charles St. Boston, MA 02114.

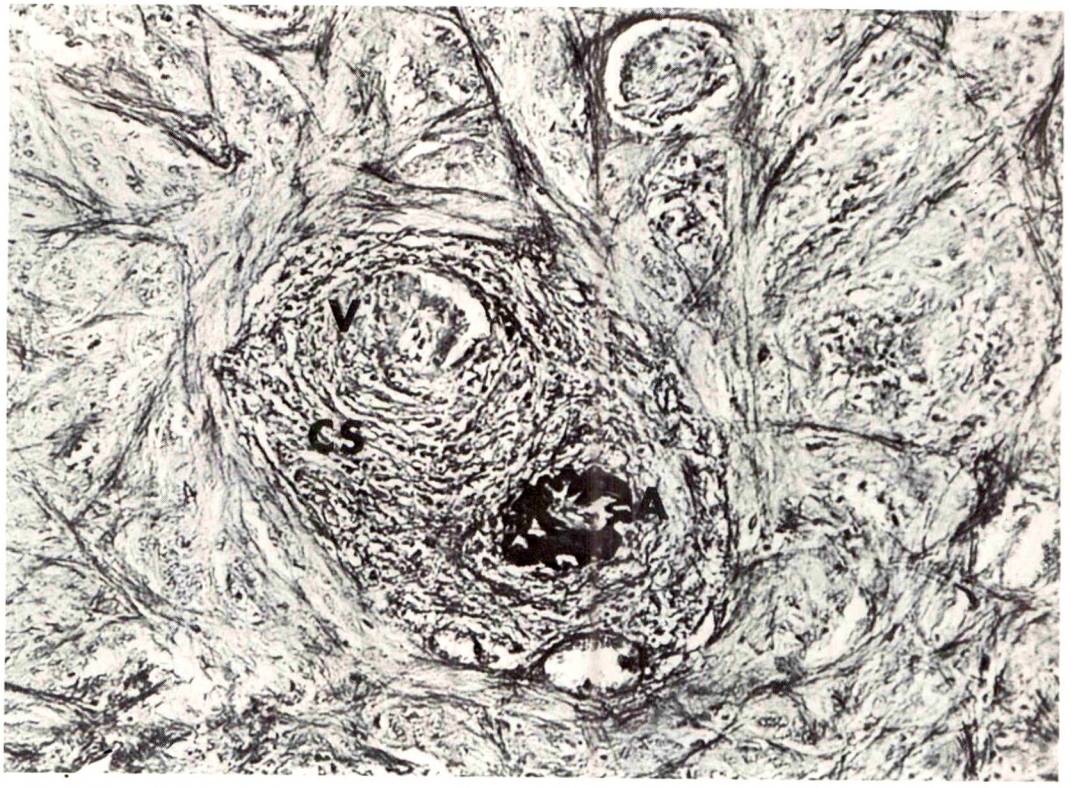


Fig. 1 (Stowe, Zakov, and Albert). Cross section of optic nerve showing occlusion of central retinal artery (A) with abnormally thickened internal elastic lamina, and central retinal vein (V), both contained within a common connective tissue sheath (CS) (Verhoeff modified elastic, ×118).

few plasma cells. Recanalization was recognized in some vessels. Other significant histologic findings included corneal edema with stromal scarring, rubeosis iridis, peripheral anterior synechiae with angle closure, anterior subcapsular and cortical cataractous changes, preretinal neovascularization with diffuse retinal atrophy, and severe optic cupping with marked optic nerve atrophy.

Discussion

In 1965, stimulated by Cogan's report,[9] Walsh[2] described eight cases of retinal vascular occlusion in patients who used oral contraceptives. Since then, many reports have implicated oral contraceptives in the development of retinal vascular occlusive disease, including occlusion of the central retinal artery, central retinal vein, cilioretinal artery and branched arterial and venous vessels.[3–8] These reports also describe retinal edema, perivasculitis, retinal hemorrhages, papillitis, optic neuritis, and retrobulbar neuritis as possible manifestations of vascular occlusive lesions related to the use of oral contraceptives.

The present report indicates a central retinal vein occlusion found on histopathologic examination to be combined with a central retinal artery occlusion. This combined form of occlusion has been described by Hayreh[10] as central retinal vascular occlusion. Our patient used oral contraceptives continuously for four years. There were no thromboembolic predispositions apparent for conditions

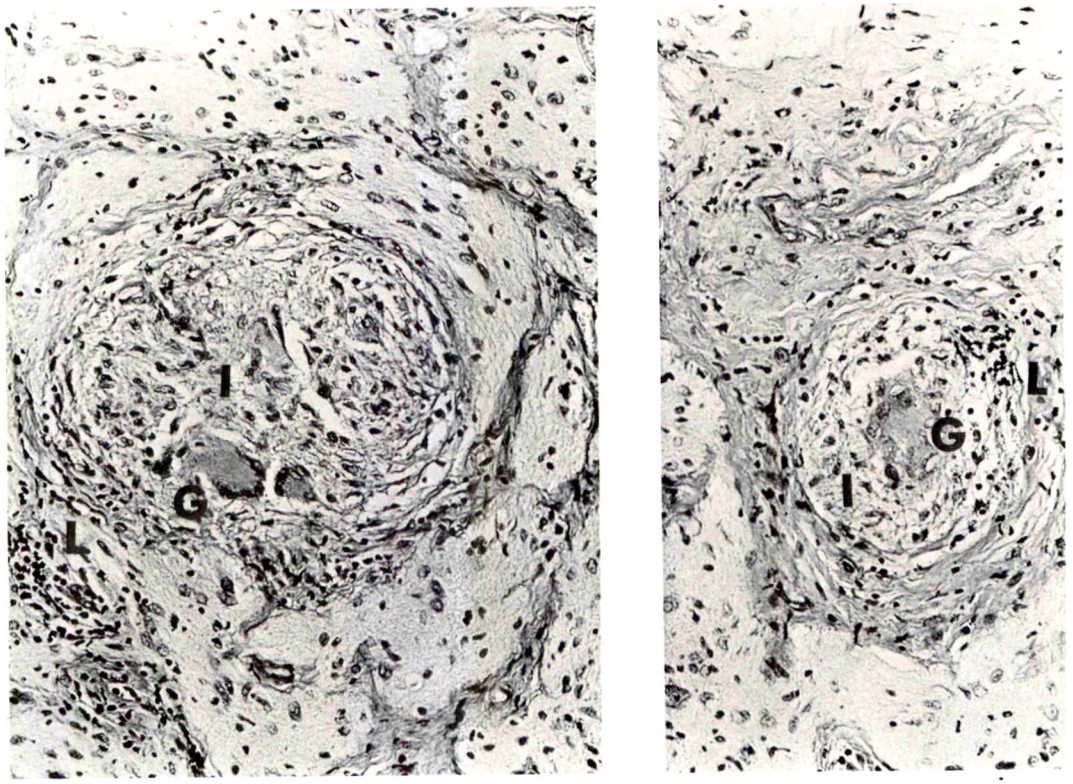


Fig. 2 (Stowe, Zakov, and Albert). Occluded retinal vessels in cross section of optic nerve demonstrating severe intimal hyperplasia (I), giant cells (G), and lymphocytes (L) (PAS, ×190).

known to be associated with vascular intimal proliferation, such as scleroderma, periarteritis nodosa, Wegener's granulomatosis, temporal arteritis, Takayasu disease, Buerger disease (thromboangiitis obliterans), or syphilis. We believe, therefore, that our patient's central retinal vascular occlusion is related to the use of oral contraceptives.

The pathogenesis of clinical retinal vascular complications secondary to oral contraceptives has been largely speculative and lacks specific pathologic correlation. Our histopathologic findings reveal occlusion of both central retinal vessels and their branches as a consequence of marked intimal proliferation. Irey and associates[11,12] reported similar intimal proliferative changes with and without thrombosis involving other systemic vessels in women who died of acute thromboembolic disease related to use of oral contraceptives and pregnancy. They suggested that female reproductive hormones were the common etiologic factor that induced endothelial hyperplasia. Histopathologic findings in intracranial vessels have also been described in women who died of strokes while taking oral contraceptives.[13–15] Altshuler, McLaughlin, and Neubuerger[13] reported irregular endothelial cell proliferation with variable occlusion associated with an inflammatory reaction consisting of lymphocytes and plasma cells. Dindar and Platts[14] and Poltera[15] described endothelial proliferation with variable vessel wall necrosis, fibrin clots, and elastic degeneration of

small intracranial arteries. Lee, Donovan and Mukai[16] studied the ocular effects of estrogens on rabbits, and observed histologically thrombosis of ophthalmic veins with fibrinoid necrosis in ciliary and choroidal arteries.

The histopathologic findings in our patient support the mechanism of a primary intimal proliferation with variable occlusion and thrombosis as a cause of retinal vascular occlusive disease associated with oral contraceptives. The presence of associated chronic inflammatory changes with giant cells most likely represents a prolonged reaction to a vascular lesion with removal of hemorrhagic, necrotic, and thrombotic debris. The pathologic studies done in the cited cases of systemic and intracranial vascular occlusions were all performed within days to several weeks of the initial clinical event, and occasionally demonstrated a polymorphonuclear vascular infiltrate. Only Altshuler, McLaughlin, and Neubuerger[13] reported a chronic lymphocytic infiltrate associated with intracranial vascular occlusion, after a clinical course of one week. However, our patient sustained a more chronic vascular injury for at least 12 months before enucleation and histologic examination.

Summary

A 40-year-old woman took oral contraceptives for four years. She developed a vascular glaucoma and one year later the eye was enucleated. No other apparent cause for the occlusion was present. The vascular occlusion consisted of a combined central retinal artery and vein occlusion with severe intimal hyperplasia. An intravascular granulomatous reaction is attributed to chronic vascular injury.

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OCULAR RIGIDITY IN KERATOCONUS

C. STEPHEN FOSTER, M.D., AND GILBERT K. YAMAMOTO, M.D.

Boston, Massachusetts

Keratoconus is a central, noninflammatory, usually bilateral ectasia of the cornea, of unknown cause. Visual impairment, from the irregular myopic astigmatism characteristic of keratoconus, is usually noted in adolescence. The reported corneal histopathology includes decreased numbers of normal collagen fibrils, keratocytes with membrane anomalies, fragmentation of the epithelial basement membrane, fibrillation and disintegration of Bowman's membrane, and degenerative changes of the basal epithelial cells.[1,2] Kim and Hassard[3] reported decreased levels of glucose-6-phosphate dehydrogenase in keratoconus corneas, and Robert and associates[4] found relative decreases in hydroxylation of lysine and in glycosylation of hydroxylysine, decreased total collagen, and increased structural glycoprotein.

Hartstein[5] reported 12 cases of contact lens-induced astigmatism; in one patient keratoconus developed in one eye. Subsequently, further reports of keratoconus developing in patients wearing hard contact lenses were published.[6–9] Hartstein and Becker[10] investigated the ocular rigidity coefficient, E (formerly K), of three groups of hard contact lens wearers: (1) patients with no development of astigmatism or keratoconus, (2) patients in whom astigmatism developed while wearing contact lenses, and (3) patients in whom keratoconus developed while wearing contact lenses. They found that patients in whom no corneal warping developed had normal coefficient of ocular rigidity, patients in whom astigmatism developed had intermediate values for E, and those in whom keratoconus developed had unusually low coefficients of ocular rigidity. They concluded that at least one type of keratoconus may be related to long-term wearing of corneal contact lenses by patients with unusually low coefficients of ocular rigidity. Davies and Ruben[11] stated that ocular rigidity seemed to be abnormally low in keratoconus.

The purpose of our study was to investigate the hypothesis that in keratoconus the deformability of the corneoscleral envelope is greater than normal, that is, that the coefficient of ocular rigidity is abnormally low.

MATERIAL AND METHODS

The coefficient of rigidity was determined in 84 unoperated eyes of 55 patients with keratoconus, in both eyes of 40 normal age-matched volunteers, in 28 eyes of 24 patients after penetrating keratoplasty for keratoconus, and in 11 eyes of 11 patients after penetrating keratoplasty for corneal scars or dystrophies.

Diagnostic criteria for keratoconus in our study included asymmetric astigmatism with lack of parallelism of the images of the mires of the Javal keratometer, plus two or more of the following findings: (1) complete or incomplete Fleisher ring, (2) distortion of keratoscopic figures, (3) typical morphologic appearance of conical cornea, (4) apical thin-

From the Cornea Service, Massachusetts Eye and Ear Infirmary and the Department of Cornea Research, Eye Research Institute of Retina Foundation, Boston, Massachusetts. This work was supported in part by Research Grant EY-05213, Program Project EY-00208, Institutional National Research Service Award EY-07018, Biomedical Research Support Grant PHS 5S07RR05527 from the National Eye Institute, National Institutes of Health; and in part by the Massachusetts Lions Eye Research Fund, Inc.

Reprint requests to C. Stephen Foster, M.D., Eye Research Institute of Retina Foundation, 20 Staniford St., Boston, MA 02114.

ning, (5) apical scarring, (6) ruptures in Descemet's membrane, (7) vertical stretch lines in the posterior cornea, (8) glistening luster reflex from the endothelium, and (9) annular dark shadow reflex seen with the ophthalmoscope.

None of the patients with keratoconus had an associated ocular or systemic disease or abnormality. None exhibited hypermobility of the joints as evaluated according to Wynne-Davies[12] and Robertson.[13]

Whether penetrating keratoplasty might alter ocular rigidity coefficient in nonkeratoconus eyes or in keratoconus eyes without severe corneal thinning, was investigated by determination of E in such patients after penetrating keratoplasty. The postoperative E determinations were made at various time intervals (from four weeks to three years), with and without the running 10-0 suture (Ethilon) in place.

Student's *t*-test was used as the statistical instrument to test the null hypothesis in comparing the differences of mean ocular rigidity values.

Ocular rigidity coefficient, E, was calculated using the Friedenwald nomogram[14]; intraocular pressure values were determined by applanation tonometry and by Schiøtz tonometry with a 5.5-g weight. For applanation tonometry, the splitting prism dividing line was positioned at a 43-degree angle to the major axis of corneal astigmatism, as determined by keratometry.

RESULTS

The mean E for all unoperated patients with keratoconus was not significantly different from that of our normal study sample (Table 1). Stratification of the patients with keratoconus according to the degree of corneal thinning, as judged by slit-lamp examination, revealed that unless the cornea were thinned by 60% or more, the mean E did not differ significantly from the normal study sample values. In the presence of thinning greater than 60% of the corneal thickness, however, the mean E was $0.0053^{mm^{-3}} \pm 0.0025$, significantly lower than in any other group in our study ($P < .001$). Finer

TABLE 1

MEAN COEFFICIENT OF OCULAR RIGIDITY VALUES

Subject	No. of Eyes	No. of Subjects	Ocular Rigidity* Mean	SD	SEM
Unoperated					
Normal	80	40	0.0240	±0.0037	±0.0004
Keratoconus	84	55	0.0216	±0.0087	±0.0009
No thinning	42		0.0226	±0.0086	±0.0013
10-60% thinning	39		0.0213	±0.0085	±0.0014
>60% thinning	3†	3	0.0053‡	±0.0025	±0.0020
Postoperative Keratoconus					
0-60%.thinning	28	24	0.0236	±0.0073	±0.0014
Other corneal disease Keratoconus	11	11	0.0231	±0.0061	±0.0018
>60% thinning	3†	3	0.0216	±0.0087	±0.0050

*SD designates standard deviation; SEM, standard error of the mean.
†Same three patients, tested before and after operation.
‡Significant difference from normal ($P < .001$).

substratifications on the basis of slit-lamp evaluation or on the basis of pachometry readings was not helpful correlating corneal thinning with ocular rigidity coefficient measurements.

The mean E of the three eyes with greater than 60% thinning reverted to normal after penetrating keratoplasty; the mean postoperative value was significantly greater than the preoperative mean ($P < .001$) (Table 1), and not significantly different from the mean E value for the normal study sample.

In determinations of the coefficient of ocular rigidity after keratoplasty, the timing of the measurement and the presence or absence of the suture had no significant effect. In the 11 eyes with corneal scars or hereditary dystrophies, the mean postoperative E value was not significantly different from the mean E value of our normal study sample.

In the 28 eyes of patients with keratoconus, but without severe thinning that underwent penetrating keratoplasty, the mean E was not significantly different from the mean E of the unoperated eyes with keratoconus and without severe thinning. It was also not significantly different from the mean E for the normal study sample or from the mean postoperative E in nonkeratoconus eyes.

Ocular rigidity coefficient was determined preoperatively and postoperatively in three patients with keratoconus without severe corneal thinning, and in six patients with corneal disease other than keratoconus (Table 2). No significant differences were found between the individual preoperative and postoperative values for these patients.

Discussion

This study shows that 93% of the keratoconus study sample patients (without other recognizable systemic or ocular disease) have ocular rigidity coefficients greater than $0.010^{mm^{-3}}$. If the three patients with greater than 60% corneal thinning are excluded, 96% of the keratoconus patients in this study have ocular rigidity coefficients greater than $0.010^{mm^{-3}}$.

TABLE 2

PREOPERATIVE AND POSTOPERATIVE OCULAR RIGIDITY COEFFICIENTS IN PATIENTS WITH KERATOCONUS AND OTHER CORNEAL DISEASE*

Patient No.	Diagnosis	E (mm^{-3}) Preoperative	E (mm^{-3}) Postoperative
1	Keratoconus	0.036	0.036
2	Keratoconus	0.017	0.016
3	Keratoconus	0.015	0.016
Mean		0.0227	0.0227
SD		±0.0116	±0.0115
SEM		±0.0067	±0.0067
4	Scar	0.021	0.022
5	Scar	0.030	0.033
6	Scar	0.025	0.032
7	Dystrophy	0.026	0.026
8	Scar	0.042	0.050
9	Dystrophy	0.016	0.016
Mean	Mean	0.0267	0.0298
SD	SD	±0.0089	±0.0117
SEM	SEM	±0.0036	±0.0048

*SD designates standard deviation; SEM, standard error of the mean.

Friedenwald[14] found that in a population of normal volunteers, the range of ocular rigidity coefficient E was 0.002 to 0.055^{mm-3}. He found that the mean E in people between 15 and 50 years, with axial refractions between +2.0 diopters and −1.0 diopters and corneal curvatures between 7.5 mm and 7.9 mm was 0.021^{mm-3}, with a range of 0.006-0.037^{mm-3}. He documented that the mean E was greater in study samples of people older than 50 years than in younger populations; less in study samples of axially myopic individuals than in emmetropic or hyperopic groups; greater in study samples of patients with corneal curvature radii less than 7.5 mm than in sample groups with corneal curvature radii greater than 7.5 mm; and corneal astigmatism had no effect on the measurements and calculations of E.

Friedenwald believed that the viscoelastic mechanical resistance of the normal cornea to deformation was small, and that ocular rigidity determinations using Schiøtz tonometry in normal eyes gave a reasonable approximation of the deformability of the corneoscleral envelope. Woo[15] predicted from theoretical calculations, that a significantly thinned cornea would be more easily deformable, and that errors would occur in intraocular pressure measurements by Schiøtz tonometry and in calculations of ocular rigidity. Ehlers, Bramsen, and Sperling,[16] in cannulation experiments, found that corneal thinning introduced artifact into intraocular pressure determinations by applanation tonometry. Kolker and Hetherington[17] believe that in the normal eye, the technique of determination of ocular rigidity by the combination of applanation and Schiøtz tonometry is subject to less error and artifact than that technique using two Schiøtz tonometry readings with two different weights. Moses and Grodzki[18] emphasized that measurement of resistance of the eyeball to distention by combined applanation and Schiøtz tonometry may be seriously contaminated by expulsion of blood from the eye, which results in underestimating the distention resistance or ocular rigidity, compared to estimation of the rigidity coefficient by two Schiøtz readings.

The effect of the measurement errors and artifacts on ocular rigidity coefficient estimations in keratoconus is unknown. It is difficult to imagine that the true viscoelastic properties and characteristics of eyes with keratoconus can be correctly identified with currently available clinical techniques for estimation of ocular rigidity coefficient.

Despite these limitations we have shown that most keratoconus patients in our study sample have apparent ocular rigidity coefficients greater than 0.010^{mm-3} a value believed by previous workers to represent abnormally low ocular rigidity.[5] We believe that whenever the keratoconus cornea is significantly thinned (greater than 60%), the calculated ocular rigidity coefficient is abnormally low. Replacement of the markedly thinned cornea by keratoplasty results in normal ocular rigidity coefficient estimations.

The cause of keratoconus is complex and variable. The keratoconus population is herterogeneous with respect to associated diseases, joint hypermobility, and lysinonorleucine collagen crosslinking.[19] We believe this population is heterogeneous with respect to ocular rigidity. We do not believe, however, that the evidence for the hypothesis of abnormally low rigidity of the ocular coats in most patients with keratoconus is convincing.

Summary

The coefficient of ocular rigidity was determined in 84 unoperated eyes of 55 patients with keratoconus, in both eyes of 40 normal age-matched volunteers, in 28 eyes of 24 patients after penetrating keratoplasty for keratoconus, and in 11 eyes of

11 patients after penetrating keratoplasty for corneal scars or dystrophies. The technique for determinations of the coefficient of ocular rigidity that should be least affected by the many potential artifacts in such determinations in patients with keratoconus was used. The calculated apparent coefficient of ocular rigidity for patients with keratoconus who had corneal thinning greater than 60% was artifactually low. This artifact was eliminated if the thinned cornea was replaced with penetrating keratoplasty, after which the determined coefficient of ocular rigidity for the eyes of these patients was normal. Of the remaining patients 96% with keratoconus had coefficients of ocular rigidity greater than $0.010^{mm^{-3}}$, and the mean coefficient of ocular rigidity of all keratoconus study patients with corneal thinning of less than 60% was not significantly different from the normal study sample. Although keratoconus patients may be heterogeneous with respect to ocular rigidity, our data do not support the generalization that most patients with keratoconus have an abnormally low ocular rigidity. We do not believe the current techniques for determination of ocular rigidity coefficients accurately reflect the true viscoelastic properties of eyes with keratoconus.

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A COMPARISON OF PENETRATING KERATOPLASTY AND LAMELLAR KERATOPLASTY IN THE SURGICAL MANAGEMENT OF KERATOCONUS

JAMES M. RICHARD, M.D., AND DAVID PATON, M.D.
Houston, Texas
AND
ANTONIO R. GASSET, M.D.
Gainesville, Florida

We report herein the results of two surgical procedures currently being used in the surgical management of keratoconus; penetrating keratoplasty and lamellar keratoplasty.

MATERIAL AND METHODS

Data were collected from the medical records of 100 consecutive cases operated between 1972 and 1977. Dr. Paton's series at Baylor College of Medicine constituted 50 eyes that received penetrating keratoplasty; there were 44 patients, of whom 24 were male and 20 were female. The ages ranged from 13 to 65 years for the males, and from 16 to 69 years for the females. The average age was 35 years.

Dr. Gasset's series at the University of Florida included 50 eyes that received lamellar keratoplasty. There were 45 patients of whom 23 were male and 22 were female. The ages ranged from 20 to 52 years for the males and from 17 to 65 years for the females. The average age was 31 years.

With few exceptions both series included the same indications for surgery: inability to wear a keratoconus contact lens because of marked corneal irregularity from the conical cornea, central corneal scarring, and inadequate best-corrected visual acuity. Patients selected for lamellar keratoplasty could not have deep stromal scarring or persistent hydrops of the cornea, and patients for penetrating keratoplasty could not have less than half-normal corneal thickness in the recipient zone for the graft. In two of the patients who received penetrating keratoplasty, there had been previous thermokeratoplasty. Four of the patients who received lamellar keratoplasty had also received thermokeratoplasty without lasting benefit.

Of those patients who received penetrating keratoplasty, the grafts in 2% were 7.0 mm, 80% were 7.5 mm, 14% were 8.0 mm, and 4% were 8.5 mm in diameter. Of those patients who received lamellar keratoplasty, 16% were 8.0 mm, 36% were 8.5 mm, 36% were 9.0 mm, 10% were 9.5 mm, and 2% were 10.0 mm in diameter.

The surgical techniques have been described elsewhere for both penetrating keratoplasty[1] and lamellar keratoplasty.[2] In each operation of both series, the entire procedure was done by the same surgeon (D. P. for the penetrating keratoplasty and A.R.G. for the lamellar keratoplasty). In most cases donor tissue was preserved in McCarey-Kaufman medium[3] or was from an eye that had been enucleated within 12 hours before keratoplasty. Two of the eyes that underwent lamellar keratoplasty received cryopreserved donor tissue.

The donor button sizes used in the method of penetrating keratoplasty for keratoconus were 7.0 to 8.5 mm in diameter, and most were 7.5 mm. The graft and the recipient defect were the same size. With a trephine, a deep groove was made

From the Cullen Eye Institute, Baylor College of Medicine, Houston, Texas (Drs. Richard and Paton); and the University of Florida, Gainesville, Florida (Dr. Gasset).

Reprint requests to James M. Richard, M.D., Department of Ophthalmology, Chidlren's Hospital National Medical Center, 111 Michigan Ave., N. W., Washington, D. C. 20010.

in the cornea, surrounding the cone but centered as much as possible. The anterior chamber was entered with a razor-blade knife, and the button was cut by using curved keratoplasty scissors. The donor tissue was then held in place with four temporary cardinal sutures of 8-0 black silk. The graft was secured with a continuous 10-0 nylon suture with four to five tissue bites per quadrant, variation depending on the size of the graft. The four cardinal sutures were removed sequentially as they were encountered in the process of placing the continuous suture. The nylon suture was then tightened, temporarily secured with a triple-thrown hitch, and retightened after the anterior chamber had been reformed with balanced salt solution. Finally, the single knot was tied and buried. Total operating time was 45 minutes.

In the lamellar keratoplasty procedure we used a Flieringa ring, which was secured using four 5-0 dacron episcleral sutures. A trephine made a superficial mark that was deepened 360 degrees to just anterior to Descemet's membrane. A small Paufique knife blade was used to extend the incision centrally about 3 mm to create a lip of cornea for grasping with two forceps. The cornea was then sheared along a stromal plane just anterior to Descemet's membrane. The endothelium of the full-thickness donor cornea was gently removed with a wet sponge (Weck-cel); the corneal graft was cut with the same size trephine as for the recipient bed. Graft diameters ranged from 8.0 to 10.0 mm, with the majority of grafts being either 8.5 or 9.0 mm in diameter. Four cardinal sutures of 8-0 black silk were placed, and a limbal paracentesis was performed with a 40-gauge needle. A continuous 10-0 nylon suture was placed with at least four loops per quadrant in an 8.5-mm graft, and six to eight tissue bites per quadrant were used in larger grafts. The cardinal sutures were removed and the nylon suture was tightened, tied, and buried. The anterior chamber was allowed to reform by aqueous secretion. Total operating time was about 2½ hours.

The postoperative care in both series was similar, though mydriaticcycloplegic drops were used four times a day following penetrating keratoplasty, whereas they were not used after lamellar keratoplasty. Topical corticosteroids were applied four times a day after both procedures. Suture removal was generally done ten months after penetrating keratoplasty, and three months after lamellar keratoplasty. Final visual correction was provided once the sutures had been removed and the refraction was reproducible on two office visits. Keratometry was recorded at this time.

Results

The final refraction, visual acuity, and keratometry were taken from the records of both surgeons or from information supplied by referring ophthalmologists. The follow-up ranged from six months to four years, with the average being two years.

Of the patients who received penetrating keratoplasty, 88% achieved corrected visual acuity of 6/9 (20/30) or better. Of those who received lamellar keratoplasty, 62% had corrected visual acuity of 6/9 (20/30) or better. Final visual acuity between 6/12 (20/40) and 6/18 (20/60) was noted in 4% of patients who had penetrating keratoplasty, and 32% of patients treated with lamellar keratoplasty were in this range. However, for final corrected visual acuity between the range of 6/6 (20/20) and 6/12 (20/40) (visual acuity required by most states for driving an automobile), 90% of the patients treated with penetrating keratoplasty and 80% of those who received lamellar keratoplasty attained visual acuity of this degree. Both series had 6% of the patients with final visual acuity between 6/30 (20/100) to

6/60 (20/200) because of reasons noted below (Fig. 1).

For patients who underwent penetrating keratoplasty, best-corrected visual acuity was achieved in 33% using spectacles, 33% using a contact lens, and 34% using either spectacle correction or contact lenses. Of those patients who received lamellar keratoplasty, best-corrected visual acuity was obtained with spectacles in 90% and with a contact lens in 10%. Patient acceptance of contact lenses in both groups was excellent.

Corneal astigmatism was derived from keratometry performed after all suture had been removed. Of the penetrating keratoplasty patients, 26% had less than +3.00 diopters of astigmatism; of the lamellar keratoplasty patients, 43% had less than +3.00 diopters. Between the range of +3.00 and +6.00 diopters were 48% of the penetrating keratoplasty series, and 46% of the lamellar keratoplasty series. More than +6.00 diopters of corneal astigmatism were found in 26% of the penetrating keratoplasty patients, whereas this much corneal astigmatism was noted in only 11% of the lamellar keratoplasty patients (Fig. 2). No keratometry was available on four patients in each series.

Wound and suture problems were the most frequent causes for reparative surgery in both series, being about 10% in each. Infection causing loss of the graft and necessitating penetrating keratoplasty occurred in two patients who received lamellar keratoplasty. Vascularization of the graft was noted in one patient in each series. Increased intraocular pressure attributed to corticosteroid use was noted in two patients in each series. Allograft reaction occurred in two patients in each series and they responded well to topical corticosteroids. Cataracts progressed following keratoplasty in two of the older patients in each series. One patient in the penetrating keratoplasty group and two patients in the lamellar keratoplasty group were thought to have lens changes secondary to corticosteroid use. An iatrogenic cataract was induced in one patient who underwent penetrating keratoplasty when the lens capsule was penetrated at the time of surgery. Folds in Descemet's membrane were noted in 10% of patients who underwent lamellar keratoplasty; these resolved in time.

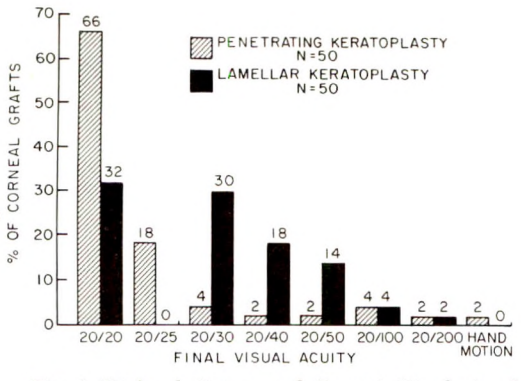


Fig. 1 (Richard, Paton, and Gasset). Final visual acuity in both series.

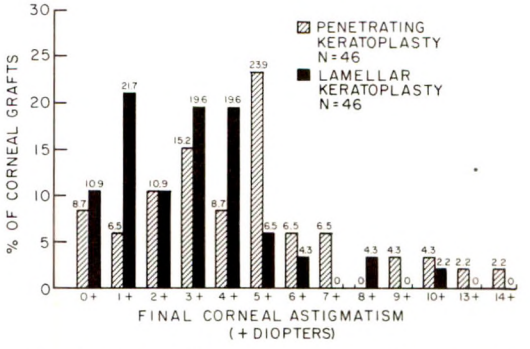


Fig. 2 (Richard, Paton, and Gasset). Final corneal astigmatism in both series.

Discussion

Most methods proposed for the surgical management of keratoconus have been abandoned for newer techniques. Though keratoplasty has a high percentage of success, any patient who receives it, whether lamellar or penetrating, must understand

that the outcome of the graft depends mainly on close follow-up care, preferably by the ophthalmologist who performed the surgery.

The decision as to which procedure is used, lamellar keratoplasty or penetrating keratoplasty, must be made knowing the limitations of each. Generally, the technique of lamellar keratoplasty is more demanding in terms of the surgeon's patience, specialized training, and operating time. Though no perforation was encountered during lamellar keratoplasty in the series reported here, this complication is possible during surgery. If Descemet's membrane is cut, conversion to penetrating keratoplasty becomes mandatory. The eye must then receive a fresh donor button with a diameter 1.0 to 2.5 mm larger than had penetrating keratoplasty been the intended operation. Large penetrating graft size is associated with increased likelihood of graft rejection, and therefore requires increased and more prolonged topical corticosteroid therapy, with inherent risks. Similarly, if a large graft fails, regrafting must be within the opaque donor tissue (worsened prognosis) or the same size as the first graft.

Lamellar keratoplasty has a tendency for some wrinkling of Descemet's membrane at the interface between the donor tissue and the recipient, thereby decreasing the optical clarity of the graft. Though these folds tend to become less pronounced after one or two years, the corneal anatomy often has some distortion at the interface. The lamellar keratoplasty series obtained its best-corrected visual acuity with spectacles more often than with contact lenses.

Penetrating keratoplasty also has limitations. Perhaps the greatest disadvantage is that it is an intraocular procedure, and damage to the iris, chamber angle, and lens is possible. Though no intraocular infections were encountered in this series, endophthalmitis is a possible complication. Donor tissue in this operation is more of a variable, since the viability and population of the endothelial cells are critical to graft success in penetrating keratoplasty, whereas donor endothelium is not a consideration in lamellar keratoplasty.

Less time is required for final visual rehabilitation after lamellar keratoplasty than after penetrating keratoplasty because of the earlier time that the corneal sutures can be safely removed. Spectacle correction and contact lens correction can be provided many months before removal of the nylon suture, but final and stable correction with either of these lens systems is usually a month after suture removal. (Other surgeons use interrupted sutures, often silk; they can remove these sutures much earlier, but there are also disadvantages to such suturing methods). Usually the final correction is given at four to six months in lamellar keratoplasty and at 12 months in penetrating keratoplasty.

Most keratoconus patients know how to use contact lenses before having keratoplasty, and they would do so postoperatively if the visual acuity were improved. One third of patients undergoing penetrating keratoplasty required contact lenses for best visual acuity, whereas only one tenth of the lamellar keratoplasty patients were fitted with a contact lens. Best-corrected visual acuity can be expected to be better in cases treated with penetrating keratoplasty than with lamellar keratoplasty. The mean visual acuity after penetrating keratoplasty with correction was 6/6 (20/20−), where as it was 6/9 (20/30−) following lamellar keratoplasty.

The study indicates that corneal astigmatism is less after lamellar keratoplasty than after penetrating keratoplasty. An average corneal astigmatism of + 3.25 diopters was noted in lamellar keratoplas-

ty and + 5.00 diopters in penetrating keratoplasty. This compares favorably to other reports.[4–8]

Wound strength is expected to be greater in the lamellar graft than in the full-thickness graft because of the scaffolding provided by Descemet's membrane. The 10% incidence in both series of wound dehiscence requiring additional suturing is normal for the continuous suture technique. Occasional small, reparable wound dehiscenses are to be anticipated and almost always do well once resutured.

Both penetrating keratoplasty and lamellar keratoplasty techniques will continue to be used in surgical management of keratoconus, and will be scientifically refined as ophthalmic technology and surgical skills improve. Microsurgical control of corneal astigmatism is being given attention,[9] and the intraoperative monitoring of suture placement and tension will continue to help reduce postoperative astigmatism.

Both procedures have their place in the surgical management of keratoconus, and it is the surgeon's responsibility to determine the appropriate approach for the individual patient.

Summary

A retrospective study of patients who underwent keratoplasty for keratoconus was done in 100 consecutive cases, of which 50 were penetrating keratoplasty procedures, and 50 were lamellar keratoplasty procedures. Each case was done by the same surgeon in both series. Criteria for patient selection were essentially the same. Postoperative care differed primarily in the time before suture removal, being an average of ten months in the penetrating keratoplasty group and three months in the lamellar keratoplasty group.

Of those patients who underwent penetrating keratoplasty, the mean best-corrected visual acuity was 6/6 (20/20−) and the average corneal astigmatism was +5.00 diopters. Of those patients who received lamellar keratoplasty, the mean best-corrected visual acuity was 6/9 (20/30−), and the average corneal astigmatism was +3.25 diopters. The most frequent complications of both techniques were wound separations that responded well to resuturing.

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COMPARATIVE CLINICAL ASSESSMENT OF CORNEAL SENSATION WITH A NEW AESTHESIOMETER

R. W. BEUERMAN, PH.D., AND J. P. MCCULLEY, M.D.

Stanford, California

Determination of corneal sensibility is pertinent to the diagnosis of corneal disease with ciliary nerve involvement.[1] However, the usefulness of this test is limited by the accuracy and reliability of the instrument. A device using a calibrated nylon filament to provide a range of reproducible stimulus intensities has been designed for the clinical determination of corneal sensation.[2] In addition to its limited availability in this country, this instrument has shortcomings that restrict its usefulness, such as: (1) it cannot be carried in the pocket without risk of damage to the filament, and this results in the device being left in its case; (2) installing replacement filaments is a lengthy process; (3) because of the small diameter (0.12 mm) and mechanical properties of the nylon filament, it describes an arc of large radius when fully extended, making it tedious to approach the cornea perpendicularly. We have designed a new, simple aesthesiometer that overcomes these drawbacks and that is sensitive enough to detect small changes in corneal sensation.*

This study received further impetus from two cases of patients who were referred to the clinic with atypical dendritic ulcers, but normal corneal sensation, as tested with a tissue by the referring ophthalmologist. A clinical diagnosis of herpes simplex keratitis was made when reduced corneal sensation was shown by the aesthesiometer. The diagnoses were subsequently confirmed on viral culture.

MATERIAL AND METHODS

Two aesthesiometers were used to examine corneal sensation in this study. The first, the Cochet-Bonnet version, which is based on the design of Boberg-Ans,[2] has been used advantageously in studies examining sensation in those with normal corneas,[3] and those with corneal disease.[5–7] The wide acceptance of the Cochet-Bonnet instrument[4–7] made it desirable to compare the performance of the new aesthesiometer introduced here (Figure) with the Cochet-Bonnet. An example of hypesthesia, herpetic keratitis, was used to provide a range of testing conditions for the comparison.

The new instrument fitted into a plastic tube after the filament was withdrawn into the barrel, which allowed it to be carried in the pocket of an examination coat (Figure). The filament, which was attached to a screw, was threaded into the thumb-operated slide (Figure), making it easily replaceable. The slightly larger diameter (0.13 mm) of the nylon filament and greater mechanical stability made it less likely to droop when extended. The brass set pin on the slide fitted comfortably into the pad of the thumb or first digit, providing smooth, positive adjust-

*This instrument is available from Mr. Thomas Rowan, 8744 Cedros Ave., Panorama City, CA 91402.

From the Department of Surgery, Division of Ophthalmology, Stanford University, Stanford, California 94305. This study was supported by National Eye Institute Grant EY 02108.

Reprint requests to R. W. Beuerman, Ph.D., S018 Stanford Medical Center, Stanford, CA 94305.

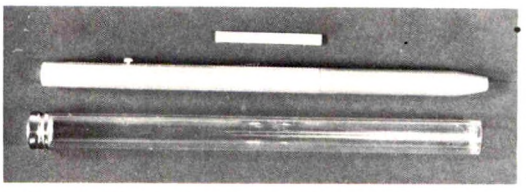


Figure (Beuerman and McCulley). The aesthesiometer and carrying tube. The bar represents 4 cm.

ment of the filament length. The measurement was then read from the barrel in either millimeters of extended filament or force (mg). This filament was calibrated on a balance (0.1 mg accuracy) using a micromanipulator to insure a perpendicular approach without unnecessary acceleration and an optical comparator so that deflections would be standardized to 5% of the length. The values obtained (68 mm, 16 mg; 60 mm, 23 mg; 50 mm, 37 mg; 40 mm, 45 mg; 30 mm, 83 mg; 20 mm, 190 mg; and 10 mm, 580 mg) fit a power function with a correlation coefficient of .99. According to the instruction book supplied with the Cochet-Bonnet instrument, the deflection force at 60 mm is 11 mg. The small difference in maximal sensitivity of the two instruments was not detectable by the patients.

The subjects of this study were seen over a period of three months in the Eye Clinic, Division of Ophthalmology, at Stanford University Medical Center. The only conditions established for their inclusion were that they had unilateral herpetic keratitis and that they were not currently taking analgesics.

Patients sat in an ophthalmic examining chair with a headrest placed so that it was in contact with the occiput, allowing the patient to remain in an upright, comfortable position. The patient was asked to fixate on an object 10 feet away. Nasal corneal sensation was determined first, followed by inferior, temporal, and central corneal sensation. The locations of the perilimbal test sites were approximately 1 mm in from the corneoscleral limbus at 3, 6 and 9 o'clock. The fixation points were varied so that these areas could be tested without retracting the eyelids. The superior cornea was tested last by having the patient fixate on an object 30 degrees below the visual axis while the upper eyelid was gently elevated with the thumb. To avoid contamination, the filament was wiped with cotton or a tissue moistened with absolute alcohol.

The testing procedure was the same for all locations and for both instruments. The patients were advised that they would feel something contact their cornea and were asked to report this. The filament was applied first completely extended, and then shortened by 2 to 3 mm at a time, until the patient reported a sensation. The instrument was held in the hand so that the tip of the filament was approximately 2 cm in front of the cornea and oriented so that a perpendicular approach would be achieved. The filament was then brought to the surface of the cornea in a smooth motion, maintaining the perpendicular approach so that the filament would not slide over the surface of the eye. Upon contact, pressure was gradually increased until the filament described an arc whose deflection was about 5% of the length. The next test was performed after the patient's response. Measurements were obtained from both instruments, usually in millimeters of filament, using this procedure with closely situated but not overlapping sites.

RESULTS

We examined directly the diagnostic usefulness of the instrument in a clinical setting, although the new aesthesiometer was used to test many individuals without any corneal disease. The results indicated that only small variations occur in normal sensitivity.[4,7]

To obtain a comparison of the performance of the two instruments, the measurements were normalized (length of filament at reading per total filament length times 100) and examined statistically (Table). In patients 1 to 4 the left cornea was involved and in 5 to 7 the right cornea; the contralateral cornea was normal in all cases. Normalization of the data was considered reasonable since the force required to bend the filament was propor-

TABLE

SUMMARY AND COMPARISON OF AESTHESIOMETER MEASUREMENTS

Patient No.	A_1*	A_2*	P†	A_1‡	A_2‡	P†
1	93.5±0.6§	93.8±4.9		39.7±5.4	43.5±11.1	
2	90.6±4.1	96.6±2.0		38.5±5.7	28.3± 6.2	<.1
3	98.2±1.8	99.8±0.7		88.8±8.3	92.5± 5.5	
4	94.7±3.3	86.0±1.7	<.1	23.4±6.0	27.5± 7.9	
5	89.1±5.2	90.6±6.2		91.9±3.7	98.0± 1.2	
6	81.7±4.0	73.3±8.1		90.3±4.8	95.0± 3.3	
7	11.7±0.0	7.0±2.9	<.2	100.0±0.0	99.0± 1.7	

*Correlation coefficient r = .98, P <.01.
†Student *t*-test for paired observations, value given if P ≤.1.
‡Correlation coefficient r = .98, P <.01.
§Mean ±S.E.M. No. = 7 in all cases.

tional to the length, and it provided a quick visual comparison of the results. In this procedure a value of 100.00 corresponded to a filament length of 60 mm for the French instrument (A_1), and 68 mm for our instrument (A_2).

Although the mean scores were similar in most cases, it was necessary to compare each data pair to determine if the two measurements from each corneal sector were statistically similar. When this was done by a two-tailed t-test for paired observations,[8] the probabilities showed that the measurements from the two instruments were essentially equivalent. In these patients, mean filament lengths for normal eyes were generally between 90 and 100 (Table). Variability in the data was greater for diseased than for normal corneas, but this was a reflection of the sometimes large differences in sensation in the various portions of the herpetic cornea.

Finally, a comparison of mean scores obtained with both instruments for the two eyes showed a highly significant correlation between the two sets of means (Table). This test, although less sensitive to variations in individual data points, indicated that the overall trend was the same for both aesthesiometers, and the mean scores on all eyes obtained by both instruments were statistically related.

DISCUSSION

We developed a new aesthesiometer that detects relatively small changes in corneal sensation that occur in patients with herpes simplex keratitis. This new instrument has several advantages in its use over the Cochet-Bonnet aesthesiometer. Paired measurements in a series of unilateral herpetic patients showed that the performance of the present instrument, when compared to the Cochet-Bonnet aesthesiometer was statistically similar. Measurements made with the aesthesiometer are subject to errors from unequal deflection, humidity, and the inability to approach a true threshold. Aside from the aesthesiometer's diagnostic value, more accurate methods overcoming these sources of error are available for basic and clinical research.[9]

The use of a diagnostic instrument capable of uncovering localized changes in corneal sensation is important in assessing cases of patients with ocular inflammation. Hypesthesia may be minimal in both degree and distribution, and thus overlooked with gross testing devices such as tissues or cotton fibers. This is

caused by the difficulty in appreciating differences in sensation between two successive stimuli of similar magnitude. When a stimulus is at threshold or just above, a small change in the stimulus magnitude will cause a greater difference in sensation. Finally, assessment of corneal sensation when evaluating cases of patients with atypical herpetic lesions may assist in diagnosis.

SUMMARY

A new version of an aesthesiometer offers particular advantages such as portability without risk of damage to the filament, easy filament replacement, and an expanded stimulus range. We compared the performance of this new instrument to that of the Cochet-Bonnet aesthesiometer in a clinical setting on herpetic patients. Using both instruments, we obtained paired measurements on the normal and diseased corneas from five test loci placed over the corneal surface. Statistical analysis of the normalized data showed that the data obtained by the new instrument were similar to those of the Cochet-Bonnet aesthesiometer.

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DELAYED HYPERSENSITIVITY TO RETROBULBAR INJECTIONS OF METHYLPREDNISOLONE ACETATE

C. G. TOBY MATHIAS, M.D., H. I. MAIBACH, M.D., H. B. OSTLER, M.D., AND M. A. CONANT, M.D.

San Francisco, California

AND

W. NELSON, M.D.

Modesto, California

System anaphylactoid and cutaneous allergic reactions are rare complications of corticosteroid therapy.[1–11] Allergic dermatoconjunctivitis has recently been reported.[12] When delayed hypersensitivity to a corticosteroid is suspected, skin tests may be performed by an occlusive patch test or intradermal injection, and the reaction evaluated in 48 to 96 hours. Discrepancies in these two techniques, that is, negative patch test but positive intradermal test, apparently result from impaired cutaneous penetration, and these differences may be overcome by increasing the patch test concentration of the suspected allergen, eliminating the need for intradermal testing. Alani and Alani[9] and Tegner[7] suggested patch testing with 25% hydrocortisone or enhanced concentrations of other corticosteroids when delayed hypersensitivity to these agents is suspected. We describe herein a patient with chronic cyclitis who developed a delayed hypersensitivity reaction to a suspension of methylprednisolone acetate. Despite appropriate patch testing, allergy could only be demonstrated by intradermal injection.

From the Departments of Dermatology (Drs. Mathias, Maibach, and Conant), and Ophthalmology (Dr. Ostler), University of California Medical Center, San Francisco, California; and Modesto, California (Dr. Nelson).

Reprint request to C. G. Toby Mathias, M.D., Room 342-A, Department of Dermatology, University of California Medical Center, San Francisco, CA 94943.

CASE REPORT

A 35-year old man with a five year history of chronic cyclitis was referred to the Department of Dermatology for suspected hypersensitivity to a methylprednisolone acetate suspension (DepoMedrol). Management of his cyclitis had consisted of various topical corticosteroid ophthalmic drops and periodic retrobulbar injections of methylprednisolone acetate. For the preceding two years the patient had noted some increase in conjunctival and episcleral erythema lasting two to three weeks, following retrobulbar injection. Six months before referral, the patient had a severe ocular inflammation after a retrobulbar injection, accompanied by deterioration in his vision. Ocular inflammation decreased and visual acuity improved with a short course of oral prednisone. Subsequently, the patient noted flares of episcleral and conjunctival erythema after topical application of the following ophthalmic corticosteroid preparations: dexamethasone phosphate; prednisolone acetate; a combined preparation of dexamethasone phosphate, neomycin, and polymyxin B; and a combined preparation of prednisolone phosphate, sodium sulfacetamide, and phenylephrine hydrochloride. An ointment containing only dexamethasone phosphate did not evoke ocular inflammation.

Examination revealed visual acuity was R.E.: 6/8 (20/25) and L.E.: 6/15 (20/50). Visual acuity improved to 6/6 (20/20) in each eye with a pinhole. The eyelids and tarsal conjunctiva were normal. The bulbar conjunctivae and episclerae of both eyes were injected, and there was an associated chemosis. A residue of material (Depo-Medrol) was evident underlying the superior temporal conjunctiva of the right eye. The anterior chamber was optically empty, and the lens showed early posterior cortical changes. The anterior vitreous of both eyes had 2+ cells and coarse clumps of cellular opacities ("snowballs") were evident inferiorly. The nerve head and vessels were normal. There was no foveal reflex.

Patch testing to a routine and preservative screening series was performed and graded according to the International Contact Dermatitis Research Group[13]; all tests were negative. Further patch tests were performed to the methylprednisolone acetate suspension (40 mg/ml), methylprednisolone acetate

0.25% cream, and 25% hydrocortisone in petrolatum. All patch tests were negative. The corticosteroid-containing ophthalmic preparations to which the patient had clinical reactions were not available for testing.

A patch test with benzalkonium chloride 0.1% (found as a preservative in the ophthalmic drops to which the patient had clinical reactions) gave a 2+ reaction. This was repeated after a two-month interval, with identical results. A biopsy of this site was interpreted as compatible with allergic contact dermatitis.

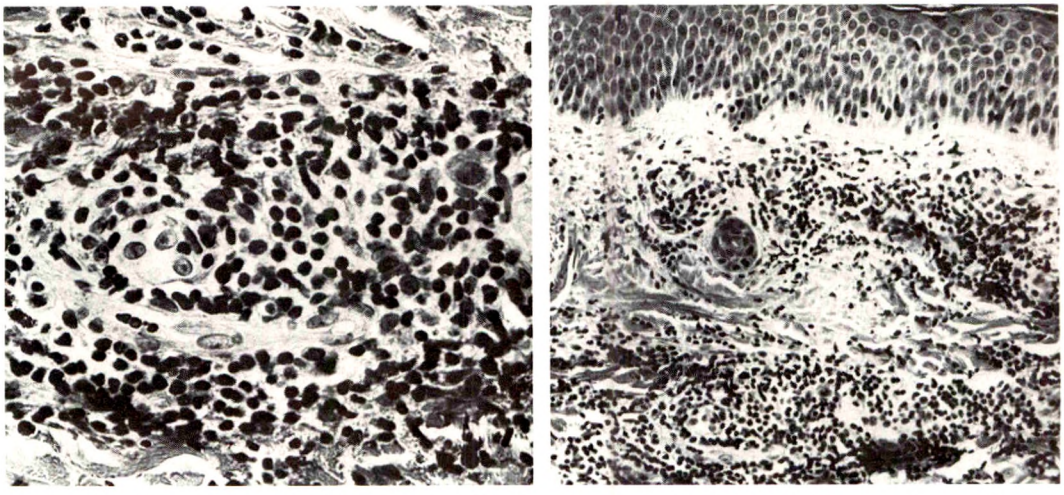
Intradermal injection of 0.02 ml of the commercial methylprednisolone acetate suspension (40 mgm/ml) produced a 10 mm erythematous papule at 48 hours. Subsequent intradermal tests were performed with 0.02 ml of 0.1%, 0.01%, and 0.001% methylprednisolone acetate powder suspended in normal saline; all produced 5- to 10-mm erythematous papules which persisted for two weeks. Similar intradermal injections with the 0.1% concentration in three controls produced only vasoconstriction and subsequent atrophy at the test site. Biopsies of two test sites showed a marked perivascular mononuclear infiltrate with numerous eosinophils (Figure). Further patch tests were performed with the remaining constituents of the commercial suspension; only a nonspecific irritant reaction to myristyl gamma-picolinium chloride (a proprietary quaternary ammonium preservative) was observed.

Information obtained from the manufacturer revealed that the only detectable impurity in methylprednisolone acetate was methylprednisolone (approximately 3%). To determine the specificity of the reaction, further intradermal tests (0.02 ml) were performed with 0.1% suspensions of methylprednisolone and prednisolone powder in normal saline. Methylprednisolone gave a positive reaction (10 mm erythematous papule); prednisolone produced an equivocal 2- to 3-mm erythematous papule. Simultaneous patch testing was performed with 25% concentrations of methylprednisolone acetate, methylprednisolone, and prednisolone in petrolatum. Patch tests were negative, indicating the inability of this technique to detect corticosteroid hypersensitivity in this patient.

Further intradermal tests were performed to commercial dexamethasone phosphate and triamcinolone acetonide injectable suspensions. The triamcinolone acetonide suspension produced 2- to 3-mm erythematous papule, while dexamethasone phosphate produced no reaction. Erythema around the injection site of triamicinolone acetonide was not observed in the controls. A careful clinical trial of periocular injections of dexamethasone phosphate was begun, and the patient tolerated this preparation.

Discussion

Adverse cutaneous or systemic reactions may rarely occur to parenteral, intra-articular, or oral preparations of hydrocortisone acetate,[1] hydrocortisone,[2] prednisone,[3,4] prednisolone acetate,[4] methylprednisolone acetate and methylprednisolone sodium succinate,[5] betamethasone,[6] and dexamethasone.[3] Allergic contact dermatitis from topical corticosteroid preparations is more



(Figure). (Mathias and associates). Low and high power magnifications of skin test biopsy, showing marked perivascular lymphocytic infiltrate in dermis, with numerous eosinophils. Mild spongiosis is present in overlying epidermis (left, ×40; right ×250).

frequent.[7-12] Tegner[7] exhaustively reviewed this subject; sensitizers included hydrocortisone, hydrocortisone acetate, hydrocortisone succinate, prednisolone, methylprednisolone, methylprednisolone acetate, triamcinolone, triamcinolone acetonide, fluocinolone acetonide, fluocortilone, betamethasone, and betamethasone valerate. Halcinonide, fluocinonide, and desonide are additionally reported sensitizers.[8] Alani and Alani[12] reported two cases of allergic dermatoconjunctivitis from betamethasone valerate.

Immediate hypersensitivity may be detected by intradermal injection followed by immediate whealing.[1,5] Delayed hypersensitivity is usually detected by patch testing. Because of occasional false-negative results, patch testing with a 10 to 25% increase over product use concentration has been recommended.[8,9] Intradermal tests, producing erythematous papules at 24 to 48 hours, may also detect delayed hypersensitivity.[1,2,4,10] Simultaneous intradermal and patch tests have been performed in only two instances; in one, only the intradermal test was positive,[4] whereas both were positive in the other.[10]

Discrepancies between epicutaneous patch and intradermal tests have been documented for several substances. Positive patch tests but negative intradermal tests have been observed with nickel,[14] paraphenylenediamine,[15] and tuberculin[16]; this is known as epidermal hypersensitivity. Conversely, negative patch tests but positive intradermal tests have been reported with nickel,[14] tuberculin,[16] neomycin,[17] and several other chemicals[14]; this is known as dermal hypersensitivity. Histologically, dermal hypersensitivity produces changes only in the dermis; epidermal changes are minimal or absent. Possible explanations for these observed differences include variable amounts of antigen, impaired cutaneous penetration, formation of different complete antigens in epidermis or dermis, differences in absolute or threshold concentration of antigen between epidermis and dermis, and rate of antigen removal. Where negative patch tests but positive intradermal tests have been observed, simply increasing the concentration of the allergen will convert a negative patch test to a positive one (neomycin).[17] The need for intradermal tests may be eliminated by patch testing at higher concentrations of antigen.

Our case demonstrates the necessity of intradermal testing for suspected contact hypersensitivity to corticosteroids even when patch tests at enhanced use concentrations are negative. Despite negative patch tests with 25% methylprednisolone acetate, hypersensitivity could be demonstrated by intradermal testing with a dilution of 0.001%. Although it may be argued that methylprednisolone acetate was totally unabsorbed after closed epicutaneous patch test application, we believe this is unlikely. Not only is methylprednisolone acetate clinically effective as a topical anti-inflammatory agent, but at least one case of hypersensitivity with a positive patch test has been reported.[10]

Precise identification of the antigenic substance in corticosteroid hypersensitivity may be difficult. It may be caused by impurities or small amounts of precursor substances in the final product,[11] or to the vehicle itself.[18] The only detectable impurity in methylprednisolone acetate was its precursor, methylprednisolone (approximately 3%); both produced positive intradermal reactions. Although purified methylprednisolone acetate was not tested, cross-reactivity is likely.

Cross-reactivity could not be convincingly demonstrated to the structurally similar corticosteroid prednisolone, implying specificity to the methylprednisolone molecule. The small erythematous

papule produced by the structurally dissimilar triamcinolone acetonide, although only equivocally positive, was surprising; no erythema was observed in controls. Clinically demonstrable cross-reactivity in corticosteroid allergy correlates poorly with structural formulae. Before alternative corticosteroids are tried, appropriate testing should be done first. Our patient had a negative intradermal test to dexamethasone phosphate; he has tolerated periocular injections of this preparation without further difficulty.

In previously reported cases, concomitant sensitization to other substances has been common. The clinical adverse reactions to the topical ophthalmic corticosteroid drops in our case may have represented contact hypersensitivity to benzalkonium chloride, a preservative found in these preparations. Delayed hypersensitivity to benzalkonium chloride is uncommon. While higher concentrations are often irritating, a reproducible positive patch test with 0.1% benzalkonium chloride suggests sensitization.

Contact hypersensitivity is a rare but recognized complication of corticosteroid therapy. When allergy is suspected, patch testing should be performed with enhanced concentrations 10 to 25% greater than product use concentration. Intradermal testing with appropriate controls should be performed if appropriate patch tests are negative.

Summary

A patient with chronic cyclitis developed hyperemia of the episcleral and bulbar conjunctival vessels after retrobulbar injections of methylprednisolone acetate suspension. Intradermal testing revealed the responsible allergen to be methylprednisolone acetate; hypersensitivity could not be demonstrated by patch testing, despite use of increased concentrations.

Acknowledgment

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USE OF DILUTE DRUG SOLUTIONS FOR ROUTINE CYCLOPLEGIA AND MYDRIASIS

CRAIG BROWN, M.D., AND CALVIN HANNA, PH.D.
Little Rock, Arkansas

The volume of solution that can be retained in the conjunctival sac is approximately 0.01 ml; however, commercial eye droppers deliver between 0.05 ml and 0.07 ml (regular eye drops).[1] A patient being prepared for refraction with eye drops containing 1% tropicamide and 10% phenylephrine receives at least four drops of solution per eye. Usually the patient will receive a total of 20 to 30 drops, which corresponds to a volume of more than 1 ml. Despite these large volumes of solution containing milligrams of drug, only a fraction of the administered drug reaches the iris and ciliary muscles to produce mydriasis and cycloplegia. Part of the problem is that many commercial eye drops are excessively irritating, and the resulting copious tearing and rapid blinking wash most of the drug out of the eye. The volume of solution retained by the conjunctival sac for more than one minute, after using commercial regular eye drops, is only a fraction of that administered.[2–4] We found that 0.005 ml and 0.01 ml (microdrops) of a 5% phenylephrine and 0.5% tropicamide mixture were both nonirritating and effective in dilating the pupil. We evaluated regular drops of nonirritating mixtures containing 1.0% phenylephrine or 0.4% hydroxyamphetamine with 0.1% tropicamide or 0.1% cyclopentolate for mydriasis and cycloplegia in clinic patients.

MATERIAL AND METHODS

Groups of ophthalmology patients requiring mydriasis and cycloplegia were randomly given eye drops of hydroxyamphetamine hydrobromide, phenylephrine HCl, tropicamide HCl, and cyclopentolate HCl. Additionally, a group of sophomore medical students were given drops in one eye as part of a physical diagnosis course. Patients excluded from this study were those with iris adhesions, no light perception in one or both eyes, or unioocular glaucoma treatment with miotics. Group 1 received 0.005 ml-microdrops of a mixture of 5% phenylephrine and 0.5% tropicamide in one eye, and regular drops (0.07 ml) of 10% phenylephrine and 1% tropicamide in the other eye. This was done using sterile PE-160 polyethylene tubing wrapped at least four times around the barrel of a 1-ml tuberculin plastic syringe and attached to the syringe through an 18-gauge needle. The syringe and tubing were filled with the drug solution and the 0.005 ml (0.004 to 0.007 ml in 25 trials) volume was delivered by squeezing the wrapped tubing between the thumb and forefinger (Fig. 1). Group 2 received 0.010 ml of a solution of 5.0%

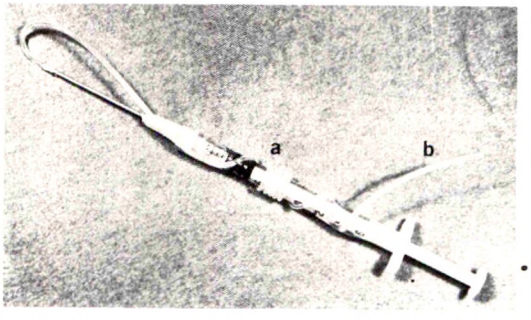


Fig. 1 (Brown and Hanna). Microliter delivery system using a syringe, needle, and attached plastic tubing. Various sizes of syringes and tubing may be used to produce desired volume. For consistent delivery of solution at least four turns (A) of the tubing around the barrel are necessary. The delivery tip (B) is kept sterile by cutting off a piece of the tip after each application.

From the Departments of Ophthalmology and Pharmacology, University of Arkansas for Medical Sciences, Little Rock, Arkansas.

Reprint requests to Calvin Hanna, M.D., Department of Pharmacology, University of Arkansas for Medical Sciences, Little Rock, AR 72201.

phenylephrine and 0.5% tropicamide in one eye from a calibrated micropipette and regular drops of 10% phenylephrine and 1.0% tropicamide in the other eye. Group 3 received regular drops of a solution of 1.0% phenylephrine, 0.1% tropicamide and 1.6% methylcellulose 400, in one eye. Group 4 consisted of healthy medical students who received one or more drops of solution containing 1.0% phenylephrine, 0.1% tropicamide and 1.0% methylcellulose 400 in one eye. These solutions were prepared by mixing commercial solutions of 10% phenylephrine, 1.0% tropicamide with 1.0% methylcellulose 400, and, where necessary, sterile isotonic saline.

Before and after the application of drops, the pupil diameter and near point were measured. If mydriasis was adequate after 45 minutes, the near point was determined, and an ocular examination was conducted which included manifest and cycloplegic refraction.

The eye drops containing a solution of 1.0% phenylephrine, 0.1% tropicamide, and 1.0% methylcellulose were requested by the clinic nurses for routine use in their patients. The following additional solutions (30 ml) were prepared and evaluated: (1) 0.4% hydroxyamphetamine and 0.1% tropicamide in Ultra Tears; (2) 1.0% phenylephrine and 0.1% cyclopentolate in Ultra Tears; (3) 1.0% phenylephrine with 0.1% tropicamide, or 0.2% cyclopentolate in one of each of the following: Adsorbobase (unknown viscosity agent), Contique artificial tears (2% polyvinyl alcohol), Lyteers artificial tears (methylcellulose derivative), Ultra Tears lubricant eye drops (1% hydroxypropyl methylcellulose), Isopto Tears (½% hydroxypropyl methylcellulose), and Liquifilm Tears (1.4% polyvinyl alcohol).

Results

Group 1 consisted of 30 randomly selected patients, 15 to 80 years old, (seven males, 23 females), and all had varying iris pigmentation. One eye received microdrops of a 5% phenylephrine and 0.5% tropicamide mixture, and the other eye received regular drops of both 10% phenylephrine and 1.0% tropicamide. The drops were given three times at five-minute intervals. The mean pupil diameter increased from 2.09 mm to 7.10 mm for the microdrops, and 2.10 mm to 7.39 mm for the regular drops 45 minutes later. Two patients who were using 1% pilocarpine drops for glaucoma therapy did not respond to the drugs and continued to receive dilating drops for several hours. Tearing and ocular irritation were experienced only by those eyes receiving regular drops. The residual accommodative ability between 45 to 60 minutes after the drops was less than 2 diopters (average 1.5 ± 0.08 SEM) in 28 patients.

Eleven male patients, 31 to 89 years old, made up Group 2. These subjects were treated as in Group 1, except a micropipette was used to accurately deliver the 0.010-ml microdrop of a 5% phenylephrine and 0.5% tropicamide mixture in one eye. Regular drops of 10% phenylephrine and 1.0% tropicamide were used in the other eye. The time course of pupillary change is plotted in Figure 2. The difference in mydriasis or cycloplegia was not statistically significant between the two eyes of any one patient, and all had a residual cycloplegia of less than 2 diopters (average 1.4 ± 0.10 S.E.M. diopters with regular drops and 1.5 ± 0.07 SEM diopters with microdrops) between 45 and 60 minutes later. Tearing and ocular irritation were experienced only in eyes receiving regular drops.

Ten patients between the ages of 31 and 89 years old made up Group 3. They received regular drops of a mixture of 1.0% phenylephrine, 0.1% tropicamide, and 1.6% methylcellulose in one eye, and regular drops of 10% phenylephrine and 1.0% tropicamide in the other eye. After an initial lag in pupillary dilation with

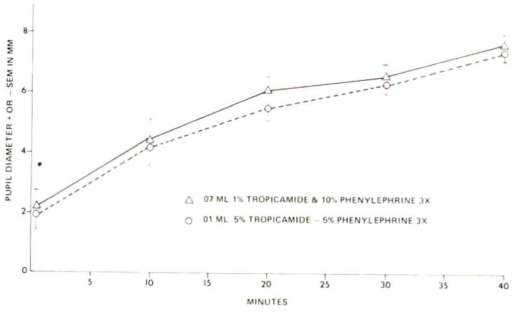


Fig. 2 (Brown and Hanna). Changes in pupil diameter by using regular drops (0.07 ml) of 1% tropicamide and 10% phenylephrine in one eye as compared to microdrops (0.01 ml) of 0.5% tropicamide and 5% phenylephrine in the other eye (Group 2). At each application time, several regular drops were given, but only one microdrop was given. Eleven subjects were used, and the mean and plus or minus standard error of the mean (SEM) is given in millimeters.

the dilute solution, there was no statistically significant difference in mydriasis between the pupils of a patient after 15 minutes (Fig. 3), and each eye had a residual cycloplegia between 45 and 60 minutes of less than 2 diopters (average 1.3 diopters with both medications). Tearing and ocular irritation were experienced only with the use of the commercial 10% phenylephrine and 1.0% tropicamide drops.

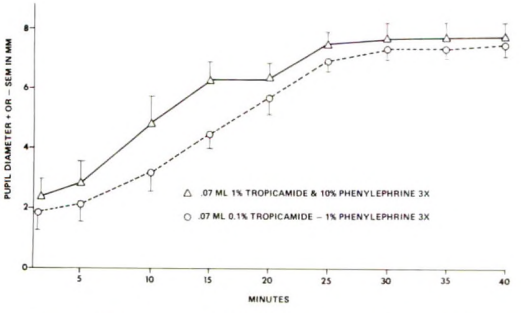


Fig. 3 (Brown and Hanna). Ten clinic patients were given regular drops of 1% tropicamide and 10% phenylephrine three times in one eye, and three regular drops of 0.1% tropicamide and 1.0% phenylephrine and 1.6% methylcellulose in the other eye (Group 3). Only at ten and 15 minutes was there a statistical difference (P = .01) between the means.

Group 4 consisted of 243 sophomore medical students who received regular drops in one eye. Of these, 107 students received a 1.0% phenylephrine, 0.1% tropicamide in 1.6% methylcellulose mixture (52 students), or Ultra Tears (55 students) three times at about five-minute intervals. No ocular irritation was noted, and the mean pupil diameter increased from 4.73 mm to 7.55 mm at 40 minutes. These students' eyes were adequately dilated for ophthalmoscopic examination. The residual cycloplegia was 2 or less diopters in 12 out of 18 students (average 1.8 diopters) measured at 45 minutes. The remaining students (136) served as the control group, and each received regular drops of 10% phenylephrine and 1.0% tropicamide. The mean pupil diameter went from 4.96 mm to 7.71 mm at 40 minutes. Most students experienced ocular irritation, and complained of being randomly chosen to receive the commercial ocular drops instead of the diluted ocular drops. Additionally, eyes receiving commercial drops of 10% phenylephrine and 1.0% tropicamide experienced an initial dilation of the conjunctival blood vessel, followed by blanching. In those eyes receiving 1.0% phenylephrine, 0.1% tropicamide, and 1.6% or 1.0% methylcellulose mixtures, the blood vessels did not initially dilate before constricting.

The nurses in our ophthalmology clinic routinely prepared patients for refraction by using drops of 10% phenylephrine with drops of 1.0% tropicamide or 1.0% cyclopentolate. They used several drops of each solution at about five-minute intervals. The patients usually responded to each drop by tightly closing their eyes. Drops of the 1.0% phenylephrine, 0.1% tropicamide in 1.0% methylcellulose solution, were studied in 50 patients. The results were similar to those shown in

Figure 3. The remaining mixtures of these drugs with commercial lubricating eye drops were tried in each of ten patients. These mixtures contained 0.4% hydroxyamphetamine or 1.0% phenylephrine with 0.1% cyclopentolate or 0.1% tropicamide in Absorbobase, Contique, Isopto Tears, Liquifilm Tears, Lyteers, or Ultra Tears. As with the other dilute mixtures above, there was an initial lag in the development of mydriasis with results similar to those shown in Figure 2. The remaining solutions (about 25 ml) and a 0.2% cyclopentolate in Ultra Tears mixture were used at random, and the extent of mydriasis and cycloplegia was not measured. Occasionally, a transient mild ocular burning and stinging sensation was reported with the 1.0% phenylephrine and 0.1% tropicamide in Contique, Liquifilm Tears, or Absorbobase, or 0.2% cyclopentolate in Ultra Tears. The nurses continued routine use of 1.0% phenylephrine with 0.1% cyclopentolate or 0.1% tropicamide in the more viscous Ultra Tears, because of the greater ease in treating the patients. Usually, one drop was applied to each eye; the excess solution remained in the conjunctival sac, and the patient was then told to blink.

Discussion

Commercial drops of mydriatic drugs, such as 2% hydroxyamphetamine, 10% phenylephrine, 1.0% tropicamide, or 1.0% cyclopentolate, contain a variety of other chemicals, such as stabilizers, preservatives, and buffers. A mixture of these chemicals and the active drug in water yield an irritant solution. To illustrate the degree of ocular irritation caused by 1.0% cyclopentolate, some ophthalmologists will first use a drop of local anesthetic. The results of our study strongly suggest the active drugs; that is, hydroxyamphetamine, phenylephrine, tropicamide, and cyclopentolate, as the major irritant in the commercial drops, since the dilute solutions with the same concentration of preservatives and buffers are not irritating.

The microdrops of 5% phenylephrine with 0.5% cyclopentolate or 0.5% tropicamide are innocuous, and as effective as regular drops of 10% phenylephrine and 1.0% cyclopentolate or 1.0% tropicamide in producing mydriasis and cycloplegia. The difficulty with using microdrops is delivering such small volumes of solution. However, it was found that dilute preparations of these drops were relatively nonirritating, and at the same time, effective when used as ocular regular drops. Although regular drops of 0.2% cyclopentolate in Ultra Tears were generally nonirritating, the 0.5% and 1.0% commercial drops of this drug lead to a burning sensation. Higher concentrations of phenylephrine, cyclopentolate, and tropicamide in select vehicles may be used to produce a faster onset of mydriasis, as long as these preparations do not lead to excessive tearing.

Pharmacokinetic studies in rabbits have indicated that an improved delivery of pilocarpine occurs when the instilled volume is reduced.[3,4] Pilocarpine solutions can induce excessive tearing which immediately dilutes the instilled drops. The reduced instilled volume,[3,4] or possibly a more dilute solution with a viscosity agent, would be more effective in delivering drug to the eye. Blinking, squeezing, or fluttering the eyelids markedly increases the washout of the instilled eye drops through the lacrimal outflow system.[5] The washout can be large enough that little drug is available for absorption,[3,6] and this loss of drug is slowed by keeping the eyelids open for several seconds after application of the drops or by gently closing the eyelids.[5] The amount of drug that is removed by the lacrimal outflow system after the application of a number of drops of 10% phenylephrine is enough

to induce systemic side effects,[7] and possible toxicity.[8] The use of dilute solutions of mydriatics and cycloplegics, or reducing instilled volume, should decrease the possibility of systemic toxicity associated with the use of these drugs in infants.[9]

Summary

Clinic patients and students were given several regular drops of commercial 10% phenylephrine HCl, and 1.0% cyclopentolate HCl or 1.0% tropicamide HCl. The drops were given three times at five-minute intervals. Mydriasis and cycloplegia were determined and compared with the results obtained by using one of the following: microdrops (0.005 or 0.01 ml) of a mixture of 5% phenylephrine HCl and 0.5% tropicamide HCl, or regular drops of mixtures of 1% phenylephrine HCl, or 0.4% hydroxyamphetamine hydrobromide with 0.1% cyclopentolate HCl, or 0.1% tropicamide in a vehicle of 1.6% or 1.0% methylcellulose 400, or artificial tears or lubricants (Absorbobase, Contique, Isopto Tears, Liquifilm, Lyteers, Ultra Tears). Except for an initial lag in the production of mydriasis with the diluted mixtures, the results were similar for all preparations. The diluted solutions produced little ocular irritation or tearing.

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STEREOSCOPIC ACUITY MEASUREMENT IN APHAKIA

MILES A. GALIN, M.D., AND IRVING BARAS, M.D.
New York, New York

The difficulties inherent in adequately correcting the aphakic eye with spectacles include magnification, chromatic aberration, spherical aberration, pin cushion distortion, visual field restriction, and ring scotoma.[1,2] Additionally, the unilateral aphakic patient encounters aniseikonia. Some unilateral aphakic patients can be trained to wear a unilateral cataract spectacle if only the central portion of the spectacle lens is used.[3] This data reinforce the concept that the main drawback to wearing a unilateral cataract spectacle is not the aniseikonia, but the swirling diplopia produced by the prismatic effect of the cataract glass as the eye moves off center. This induced prismatic effect may be corrected by arbitrarily reducing the peripheral power of an aphakic lens by 4 diopters to compensate for the increased vertex distance created by looking off center, while the spectacle remains fixed. In the unilateral aphakic patient, and the bilateral aphakic patient, however, there are no published data that support the benefits of these spectacles relative to their function, and not just their appearance.

The monocular aphakic patient usually must wear a contact lens. Because many patients cannot successfully use contact lenses, ocular surgeons have begun using intraocular lenses during cataract extraction, particularly in the elderly.

We have cared for many bilateral aphakic patients who wear a contact lens on one eye and have a pseudophakic lens in the other. Although visual acuity may be equal in both eyes, or sometimes better in the eye with the contact lens, these patients usually prefer, for mechanical reasons, the pseudophakic eye. They do not use the contact lens and slowly abandon it or request an implant in the already aphakic eye. For this reason, we compared and evaluated the binocular efficiency and visual performance, not just visual acuity, of aphakic patients corrected with spectacles, contact lenses, and intraocular lenses.

SUBJECTS AND METHODS

We studied 509 patients with visual acuity of at least 6/12 (20/40) in each eye, a visual level which was arbitrarily chosen to eliminate the effect that impaired vision has on binocular function and to be able to achieve realistic comparisons. A past history of strabismus, amblyopia, or retinal or corneal disease excluded the patient from the study. The majority of pseudophakic patients (90%) had Fyodorov Sputnik lenses, some had iris clip lenses, and a few had iris suture lenses. The majority of contact lens wearers used hard lenses (80%); the others used soft lenses.

The patients were divided into the following groups:

(1) Bilateral aphakia: corrected with spectacles; corrected with bilateral contact lenses; corrected with bilateral pseudophakes; and corrected with a contact lens in one eye and a pseudophake in the other. (2) Monocular aphakia: corrected with a contact lens; and corrected with a lens implant.

The following tests were performed on each patient: (1) prism cover measurements at distance and near; (2) near point of convergence; (3) convergence and divergence amplitudes at distance and near;

From the Departments of Ophthalmology of the New York Medical College (Dr. Galin) and Mt. Sinai Medical Center (Dr. Baras), New York, New York.
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Reprint requests to Miles A. Galin, M.D., Department of Ophthalmology, New York Medical College, 1249 Fifth Ave., New York, NY 10029.

(4) measurement of subjective angle on the synoptophore; (5) measurement of fusional amplitudes on the synoptophore using foveal targets, macular targets, and peripheral targets; (6) testing for suppression by using a Polaroid vectograph slide at distance; (7) measurement of stereoscopic acuity at distance by using a Polaroid vectograph slide; and (8) measurement of stereoscopic acuity at near by using a Polaroid Titmus test.

Additionally, we studied 19 patients for aniseikonia with the space eikonometer. Polarized tests present monocular clues that would be eliminated by random dot stereograms, but we used them because they are common and our data comparative.[4]

Results

Analysis of the data revealed that stereoscopic acuity levels yielded the most clinically useful and consistent results for judging and comparing certain aspects of binocular performance. Stereoscopic acuity at distance of one minute of arc was best achieved by the bilateral contact lens group. At two minutes of arc, although the differences between the groups decreased significantly, the bilateral contact lens wearers still performed the best. At near, the bilateral contact lens and the bilateral implant lens groups performed about equally at the 40 second of arc level (Table 1).

The monocular lens implant patients performed better than the contact lens group both at distance and near (Table 2). Space eikonometry confirmed that image sizes were larger in contact lens wearers than in lens implant wearers, but rarely more than 5%. The eikonometric measurements were not clinically significant.

Discussion

Visual acuity, stereoscopic acuity, fusional convergence amplitudes, forms and size of peripheral fields, color appreciation, image size, accommodation, degree of spherical and chromatic aberration, and refractive errors are only a few of the components of the totality of the quality of vision. We still do not know how to match and compare all these physiological variables to determine which eye has the best vision.

Stereoscopic acuity levels are a measurement of some of the higher degrees of fusion, and therefore, of the efficiency of the binocular process. Using orthoptic machines and devices such as Polaroid filters seem artificial because they do not give a true picture of real ocular function in life and space, but for comparative purposes, these devices do provide useful measurements. In theory, the use of real space tests, such as the Howard-Dohlman apparatus or the Verhoeff Stereopter, might be more acceptable, but in practice,

TABLE 1

STEREOSCOPIC ACUITY IN BILATERAL APHAKIA

Lenses	No. of Patients	Distance*		Near*	
		1 Min of Arc	2 Min of Arc	40 Sec of Arc	50 Sec of Arc
Bilateral spectacles	60	60	75	25	40
Bilateral contact lenses	45	80	87	53	80
Bilateral pseudophakes	30	50	70	50	70
Contact lens and pseudophake	98	47	64	44	58

*The numbers in each column refer to the percentage in each group able to achieve the indicated stereoscopic acuity levels at distance on a Polaroid vectograph slide and at near on the Polaroid Titmus test.

TABLE 2

STEREOSCOPIC ACUITY IN MONOCULAR APHAKIA

	No. of Patients	Distance*		Near*	
		1 Min of Arc	2 Min of Arc	40 Sec of Arc	50 Sec of Arc
Contact lens	54	48	63	22	44
Pseudophake	222	60	72	51	65

*The numbers in each column refer to the percentage in each group able to achieve the indicated stereoscopic acuity levels at distance on a Polaroid vectograph slide and at near on the Polaroid Titmus test.

their results are as obscure as those of visual function.

Contact lens wearers see larger images than do pseudophakic wearers.[5,6] The aniseikonia produced does not, in general, seem to be an impediment to fusion or function, and therefore, we question the need to reduce the power of the pseudophake for this purpose.[7]

For the components of the visual process we have analyzed the influence of contact lenses and pseudophakes on binocular function. Both result in visual performance superior to that of spectacles. Patients who have a contact lens in one eye and an implant in the other eye prefer the implant because of convenience rather than an optical or physiologic factor. Spectacles with reduced peripheral power do not compete with the superiority of contact lenses or intraocular lenses. These are the methods preferred for treatment of aphakia despite recent protestations of how good aphakic vision is with spectacles.

The use of an intraocular lens is a surgical choice. Formerly, some physicians tried to justify the use of intraocular lenses rather than contact lenses, on the basis of binocular function, eisokonia, and related categories. These considerations are more apparent than real in comparing these two types of visual rehabilitation. The implant provides as good an available optical system as is possible for aphakia. If the nature of the patient, surgeon, or eye precludes implantation, contact lenses are an adequate alternative.

SUMMARY

We performed a variety of tests to assess binocular function on monocular aphakic patients wearing contact lenses, monocular pseudophakic patients, bilateral spectacle-wearing aphakic patients, bilateral aphakic contact lens wearers, and bilateral pseudophakic patients. Stereoscopic acuity levels at distance and near when visual acuity was at least 6/12 (20/40) provided the most useful data. Pseudophakic patients and contact lens wearers performed equally well and outperformed spectacle wearers. Implant patients did not have superior stereoscopic acuity.

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TRAUMA TO THE LACRIMAL SYSTEM IN CHILDREN

FRANK A. BILLSON, F.R.C.S., F.A.C.S., HUGH R. TAYLOR, F.R.A.C.S., AND CREIG S. HOYT, M.D.

Parkville, Victoria, Australia

In 1973, McDowell[1] described the importance and methods of establishing patency of the lacrimal drainage system after injury. We describe herein the results of repair of damage to the lacrimal drainage system in patients at a children's hospital and the problem of treatment of lacrimal obstruction in children caused by congenital obstruction and other factors. All the surgery of traumatic cases was performed or supervised by one of us (F. A. B.).

We classified injuries in two groups: (1) injuries to the nasolacrimal duct, usually associated with fractures of the orbit and lateral wall of the nose including fractures of the middle third of the face, and (2) injuries to the canalicular system, most commonly avulsion injuries caused by hooks or dog bites.

MATERIAL AND METHODS

Nasolacrimal duct injuries—A dacrocystorhinostomy will usually relieve obstruction of the nasolacrimal duct caused by injury. A near-vertical incision is made through a point just medial to the midpoint between the nasion and inner canthus (Fig. 1). The orbicularis is split with mosquito forceps so that the angular vein is not incised. The margin of the orbit is revealed in the depth of the incision, and the insertion of the medial palpebral ligament is defined. Skin edges are retracted, and anterior and posterior flaps are fashioned from the lacrimal sac. One need not hesitate to divide the medial palpebral ligament close to its insertion to the frontal process of the maxilla if it improves exposure. The thin bone of the lateral wall is then removed with rongeur bone-cutting forceps to reveal the nasal mucous membrane which is then fashioned into an anterior and posterior flap. The flaps are sutured with 7-0 black silk to the respective anterior and posterior flaps of the lacrimal sac. A drainage tube is not inserted. If the medial canthal ligament has been divided, it is reconstituted with 6-0 nylon.

Age is no barrier for this procedure; the youngest child in our series was 7 months old at the time of surgery (Fig. 1).

Probing of nasolacrimal duct is done chiefly in cases of congenital obstruction and in trauma cases when the middle third of the face is fractured (the probing is helpful if done early when fractures are being reduced). However, the trauma cases reported in this series were referred late, and probing in these cases proved to be a futile maneuver.



Fig. 1 (Billson, Taylor, and Hoyt). Site of incision for dacrocystorhinostomy in a 7-month-old infant.

From the Division of Ophthalmology, Royal Children's Hospital, Flemington Road, Parkville, Victoria, Australia.

Reprint requests to Frank A. Billson, M.D., the University of Sydney, Department of Ophthalmology, Sydney Eye Hospital, Sir John Young Crescent, Woolloomooloo N.S.W. 2011, Australia.

Technique for probing of congenital nasolacrimal duct obstruction—Probing is deferred in infants until the age of 6 months unless infection is troublesome or there is a congenitally encysted mucocele requiring urgent treatment. Many cases spontaneously resolve with simple measures such as pressure over the site of the tear sac performed three or four times a day by the suitably instructed mother.

In small babies, we probe the duct under general anesthesia by means of Foster probes (Fig. 2) usually 0.6 to 0.8 mm in diameter. If there is a mucocele, the tear sac is irrigated with Neosporin until the fluid passes freely and visibly from the other punctum. The probe is then passed through the upper canaliculus and down the nasolacrimal duct. The surgeon often will encounter obstruction, experienced as a slight increase in resistance to the probe as it punctures the mucous membrane beneath the inferior turbinate and the probe is then removed and a silver lacrimal cannula of similar diameter to the probe is then passed via the upper canaliculus down the nasolacrimal duct. With a transparent plastic catheter leading from the pharynx and out the mouth to allow observation of fluid sucked from pharynx, fluorescein-stained saline is injected down the silver cannula and its appearance in the catheter verifies patency. Alternatively the face mask is removed, the infant turned on its front, with neck extended, and saline is gently injected down the cannula in the nasolacrimal duct to be observed as it drops from the nose, verifying the nasolacrimal duct has been opened. If any doubt still exists, the first probe is reintroduced into the nasolacrimal duct and a second probe is passed into the nose beneath the inferior turbinate. The surgeon can feel the first probe with the second probe, and if mucous membrane intervenes, rubbing the probes together will remove the mucous membrane obstruction. This maneuver is valuable in cases (often repeatedly probed before referral) in which one assumes the probe has passed down the nasolacrimal duct and lifted the mucous membrane beneath the inferior turbinate rather than perforated it.

Canalicular injuries—Primary repair of the severed canaliculus requires some form of splint to align the lumen of the severed ends of the canaliculus. The splint used is Silastic tubing with a 0.6-mm internal diameter (Fig. 3).

The operating microscope is useful in identifying the cut ends of the canaliculus. Retrograde placement of the pigtail probe is preferable because the risk of false passage is reduced by this method. A

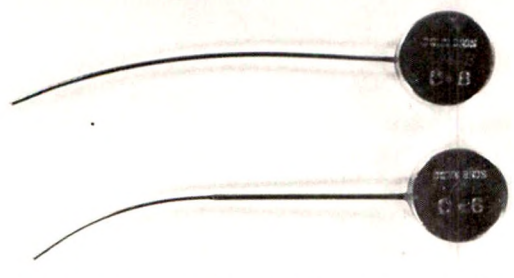


Fig. 2 (Billson, Taylor, and Hoyt). Foster probes used for probing nasolacrimal duct.

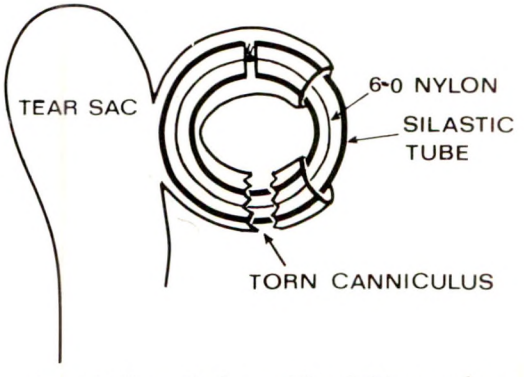


Fig. 3 (Billson, Taylor, and Hoyt). Diagram shows Silastic tubing with 0.6-mm internal diameter used as a splint to align lumen of canaliculus. 6-0 monofilament nylon holds ends of tubing in apposition to complete splint. (Tube rotated to bring knot inside upper canaliculus.)

6-0 monofilament nylon is attached to the eye of the pigtail probe (pigtail probes with hooks catch tissues and increase damages and should not be used). The 6-0 nylon is drawn through the lumen of the canaliculus by the pigtail probe. The 6-0 nylon is then attached to the Silastic tubing (down which a second piece of 6-0 nylon has been threaded) and drawn into position. The Silastic is cut and the nylon previously placed in its lumen tied to complete the circular splint (Fig. 4). The ends of the knot are cauterized and the splint moved to bring the knot into the upper canaliculus (Fig. 5) so that the knot does not rub against the globe. The splint is left in place for two to three months before being removed.

The several pericanalicular tissues are drawn together with 10-0 monofilament nylon and skin closed with 6-0 black silk sutures.

The timing of surgery depends on the presence or the absence of swelling. In most cases, the amount of swelling is not appreciable and immediate repair may be undertaken. If swelling is appreciable, a delay of one or two days may be necessary before surgery to allow the swelling to subside.

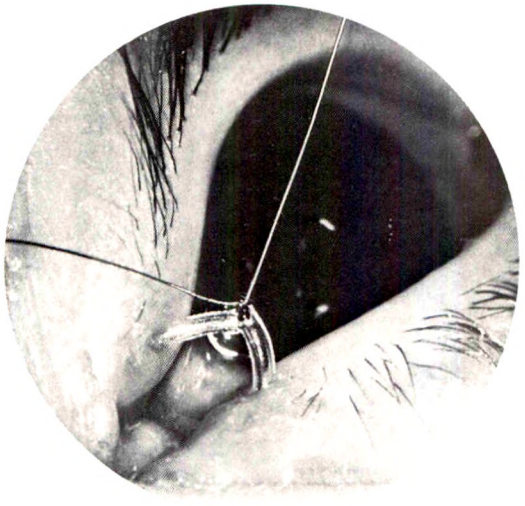


Fig. 4 (Billson, Taylor, and Hoyt). Photograph of 6-0 nylon being tied to complete the Silastic splint.



Fig. 5 (Billson, Taylor, and Hoyt). Silastic splint in situ two months after insertion. Absence of watering with splint in situ is good prognostic sign.

RESULTS

The success of repair was judged by freedom from epiphora outdoors, patency to syringing; In some cases, to determine the results, we instilled fluorescein 2% and examined the nasopharynx with cobalt blue light and held the upper eyelid away from the globe to exclude dye passage via the upper canaliculus.

Results of repair of traumatic obstruction of the lacrimal drainage system (Table 1) were contrasted with the overall results of surgical relief of lacrimal obstruction from all causes (Table 2). In this series dacrocystorhinostomy was effective in all 27 cases regardless of the cause of nasolacrimal duct obstruction. Probing was successful in 333 of 350 (95%) of the cases of congenital nasolacrimal duct obstruction, but unsuccessful in traumatic obstruction when not done at the time of fracture reduction. The follow-up period was six months to five years.

Immediate repair of canalicular injuries was effective in 12 of 16 cases. (In this series all cases referred involved injuries to the lower canaliculus.)

TABLE 1

RESULTS OF SURGICAL REPAIR AFTER TRAUMA TO LACRIMAL SYSTEM

Site	No. of Patients	Type of Injury	No. of Patients With Injuries	No. of Patients with Relief of Symptoms
Canaliculus	16	Rupture		
		Dog bite	9	
		Fall on hard object		12
		or hook	4	
		Stick thrust in eye	3	
Nasolacrimal duct	10	Fracture of orbit	9	
		Avulsion of lateral		10
		tip of nose	1	

DISCUSSION

In the children described in this study, obstruction of the nasolacrimal duct was less commonly the result of trauma than of congenital obstruction, in contrast to injuries to the canaliculi in which avulsion injuries were the predominant cause of obstruction.

In congenital obstruction of the nasolacrimal duct, the technique described for probing relieved the obstruction in almost all cases including several cases in which there had been repeated probing before referral. In the few cases in which patency had not been established, dacrocystorhinostomy was successful. In traumatic obstruction, dacryocystorhinostomy was required, and in this series, it was deferred until the child developed a mucocele. The success rate of the dacrocystorhinostomy was 100%. In all but one case, the canaliculi were patent. The exception required an indwelling Silastic tube that was placed in the canaliculi at the time of the dacrocystorhinostomy, according to the technique described by Werb[2] and recently advocated by Rogers.[3]

Trauma to the nasolacrimal duct was most often associated with fracture of the facial bones (including the middle third of the face), particularly, in car accidents (Fig. 6). Campbell,[4] who had developed macrodacryocystography since Van Der Plaats'[5] early description, analyzed the anatomy of the lacrimal drainage system with macrodacryocystograms and dissection of cadavers. He stated that obstruction of the nasolacrimal duct occurred in

TABLE 2

RESULTS OF SURGERY FOR LACRIMAL OBSTRUCTION*

Site	Operation	No. of Patients	No. of Patients With Relief of Symptoms
Nasolacrimal duct	Probing	350	333
	Dacrocystorhinostomy	27	27
Canaliculus	Pigtail probe	16	12
	Silastic tube		

*Royal Children's Hospital, Melbourne, July 1971 to January 1976.

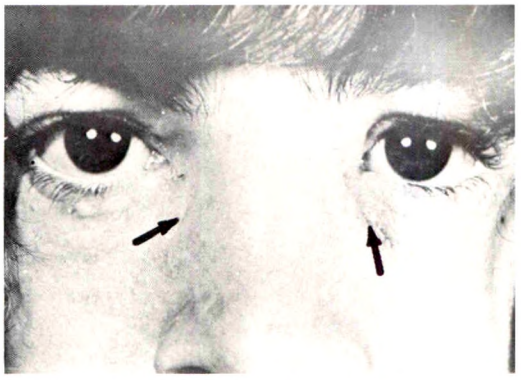


Fig. 6 (Billson, Taylor, and Hoyt). Thirteen-year-old boy, front passenger in car accident who was not wearing a seat belt, sustained middle third fractures of face and three months later had bilateral lacrimal sac abscess. Subsequent bilateral dacrocystorhinostomy (arrows point to incisions) established tear drainage. At surgery, fractures involved both nasolacrimal ducts.

12% of fractures of the middle third of the face.[6] Traumatic obstruction of the nasolacrimal duct is often overlooked initially, and it only becomes obvious with the later development of epiphora and infection. Surgery is often tedious because of the distorted anatomy, bony fragments, and callus formation. Mustarde[7] advocated dacrocystectomy for traumatic obstruction associated with fractures if infection of the tear sac is present. Our experience with children suggests that a dacrocystorhinostomy is worth attempting first. If the physician pays close attention to clinical signs and history, dacryocystography, in our experience, is unnecessary to manage nasolacrimal duct obstruction in children.

Congenital obstruction of the canaliculus is rare and is caused by a failure of canalization. If both canaliculi are extensively obstructed, surgery is usually delayed until after the age of 12 years. Symptoms in these cases are usually mild and are not attended by infection. Traumatic obstruction is usually caused by severence of the canaliculus. With traumatic obstruction of the nasolacrimal duct, delayed repair gives good results. We try to recognize canalicular injuries early, and if swelling is minimal, we perform early primary repair. If appreciable swelling is present, we delay repair for a few days to allow the swelling to subside. Successful primary repair was achieved in 12 (75%) of 16 cases.

Canalicular injuries in children in this series were most often associated with dog bites or tearing injuries caused by hooks. The dog bite was often caused by the family pet, and in most cases appeared to have been a reflex response rather than an indication of the disposition of the animal. Recognition of these injuries is sometimes difficult, and we did not hesitate to perform an examination under anesthetic to define the problem more clearly and exclude injury to the canaliculus. Sometimes the external injury to the eyelid was minimal.

Obstruction of lacrimal drainage is rarely associated with epiphora unless there is reflex irritation.[1] As long as one of the canaliculi is patent, epiphora will not be troublesome.[8] The criteria for cure was the lack of epihora in a normal warm indoor environment.[1,8]

The soft 0.6-mm internal diameter Silastic tube was left in place for two to three months and was tolerated without discomfort or complications, and the children attended school and continued participating in sports. Successful results were achieved in 12 of 16 cases according to the following criteria: no epiphora in the wind and patency to syringing. Three of these cases required surgery later for other reasons, and the canaliculus was patent to syringing in each case.

In cases with obstruction of the common canaliculus, which, in our experience, usually results from congenital absence of the canaliculi, we delay repair until after the age of 12 years, when the

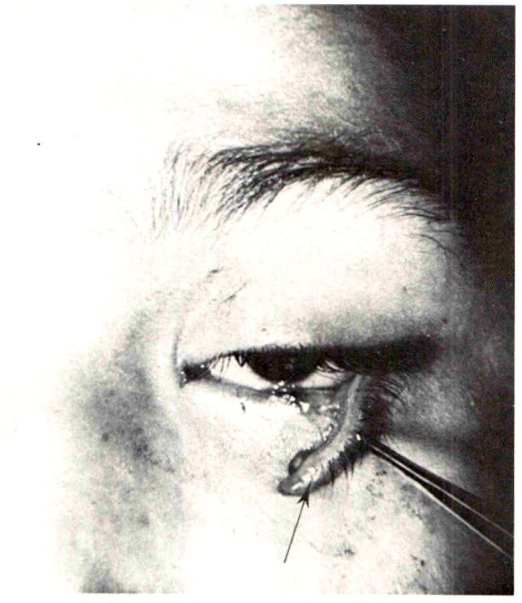


Fig. 7 (Billson, Taylor, and Hoyt). Injury of lower eyelid involving canaliculus (arrow points to punctum). Dog's tooth avulsed eyelid.

child is more cooperative and the correct management of Reinecke or Lester Jones tubes is easier.

With increasing use of the microscope and the simplification of repair by means of new materials, one should perform surgery to attempt to restore the anatomy and function of a damaged area. In early canalicular repair, canalicular function may be restored and the eyelid may be repaired (including better apposition to the eyeball) (Figs. 7 and 8).

Summary

We repaired damage to the lacrimal drainage system in a series of 393 children who had lacrimal obstruction caused by congenital obstruction or facial injuries. Delayed surgery for traumatic obstruction of the nasolacrimal duct in children, including infants, was successful in all cases.

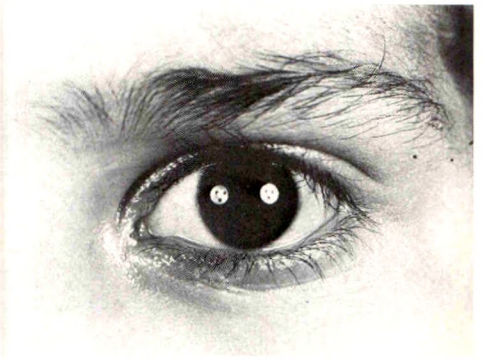


Fig. 8 (Billson, Taylor, and Hoyt). Accurate repair of ruptured canaliculus and eyelid in case depicted in Figure 7 provides anatomic and functional improvement.

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OPHTHALMIC FEATURES OF CHROMOSOME DELETION $4p^-$ (WOLF-HIRSCHHORN SYNDROME)

LLOYD M. WILCOX, JR., M.D., AND LIONEL BERCOVITCH, M.D.

Boston, Massachusetts

AND

RUFUS O. HOWARD, M.D.

New Haven, Connecticut

In 1965 Wolf and associates,[1,2] and Hirschhorn, Cooper, and Firschein[3] described patients who had partial deletion of the short arm of a B-group chromosome, but whose clinical features were somewhat different from the cri-du-chat syndrome, the only B-deletion syndrome recognized at that time. Chromosome techniques available then could not differentiate between the two clinical types, although autoradiographic studies suggested a difference.[4] Giemsa banding techniques have demonstrated that different B-group chromosomes were involved and that there were two separate anomalies.[5,6] The cri-du-chat syndrome involved a partial deletion of the short arm of chromosome 5, with a break point occurring in region 1 of the short arm, and a frequent interstitial deletion involving the two terminal bands designated $5p^-14^-15$[7,8] (Fig. 1). The Wolf-Hirschhorn syndrome is associated with partial deletion of the short arm of the fourth chromosome, designated by international convention as $4p^-16$, the number 4 denoting the chromosome, the letter p the short arm, and 16, the possible band of a typical break.[8,9] Recent reports suggest less variability with $4p^-$ than with $5p^-$, but breaks may be interstitial or terminal, possibly involving band 1 (4p11) or band 5 (4p15.2).[8,10] To date, about 40 cases of the chromosome anomaly $4p^-$ have been published; the occurrence of $4p^-$ is thought to be more rare than the reported incidence of less than 1/25,000 live births for the $5p^-$ syndrome.[11]

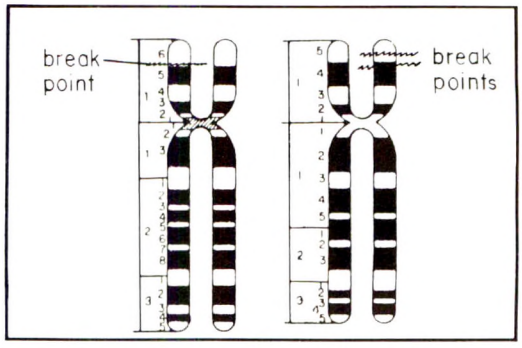


Fig. 1 (Wilcox, Bercovitch, and Howard). Banded chromosomes in metaphase $4p^-$ left and $5p^-$ right. Note the similarity and proposed breakage sites on the short arms.

We report herein the ocular findings of three patients with the $4p^-$ anomaly.

CASE REPORTS

Case 1—A white female infant weighing 2,200 g was born to a 26-year-old, gravida 3, para 2 mother at 35 weeks' gestation on March 3, 1975.

A single umbilical artery and generalized edema were noted at birth. She was transferred to the Boston Floating Hospital for Infants and Children, Boston, Massachusetts, where additional abnormalities were diagnosed. The child had generalized hypotonia, hyporeflexia, microcephaly, low-set ears, pre-auricular sinus, midline scalp defect, flat nasal bridge, micrognathia, cleft of hard and soft palate, hypoplastic nipples, ventricular septal defect, and clinodactyly of both fifth digits.

Ocular examination at 18 months (Fig. 2) revealed mild epicanthal folds with bilateral blepharoptosis,

From the Departments of Ophthalmology (Drs. Wilcox and Bercovitch), Tufts-New England Medical Center, Boston, Massachusetts; and Yale University School of Medicine, (Dr. Howard), New Haven, Connecticut.

Reprint requests to Lloyd M. Wilcox, Jr., M.D., Department of Ophthalmology, Tufts-New England Medical Center, 171 Harrison Ave., Boston, MA 02111.

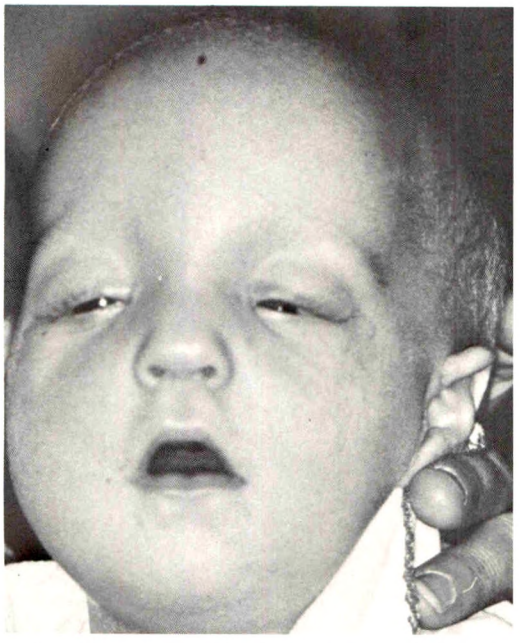


Fig. 2 (Wilcox, Bercovitch, and Howard). Case 1, age 18 months. The typical facies in $4p^-$, especially antimongoloid fissures, blepharoptosis, flat nasal bridge, and low-set ears.



Fig. 3 (Wilcox, Bercovitch, and Howard). Case 1. Rieger's anomaly; atrophy of anterior stroma, posterior embryotoxon, and ectopic pupil noted.

antimongoloid eyelid fissures, appearance of hypertelorism confirmed radiologically, and unrestricted ocular motility with an alternating exotropia of approximately 35 prism diopters. The interpupillary distance was 52 mm. The inner canthal distances measured 30 mm, and the outer canthal distances were 83 mm. She would fixate briefly with the right eye but not follow, and would not fixate or follow with the left eye. Intraocular pressure was 14 mm Hg by applanation in both eyes. The central corneas were clear for approximately 9 mm in diameter. A small band of peripheral cornea was scleralized. Both pupils were displaced nasally and slightly inferiorly. The anterior iris surface was feathery and suggested stromal atrophy because of prominent radial iris vessels (Fig. 3). There was a prominent anterior ring of Schwalbe from 3 to 9 o'clock inferiorly in both eyes. Dense iris processes were visible 360 degrees on gonioscopy, which inserted into Schwalbe's line, and the anterior chamber was deep. Both lens and vitreous were clear. The optic nerves had a pronounced elliptical shape, deep central cup, and separate emergence of arteries and veins; the inferior nasal vessels were absent. The retinal vessels were tortuous, and foveal reflexes were absent.

Sustained optokinetic nystagmus response with either eye was negative. The Schirmer tear test No. 1 was normal. Cyclopentolate refraction revealed R. E.: ×3.00 - 0.75 axis cyl 170; L.E.: +3.50 - 1.25 axis cyl 180. Patterned visual-evoked responses obtained at 1 year of age showed maximum amplitude of a 30-minute check, and background noise consistent with poor visual acuity. Signals were obtained at 16 flashes per second, suggesting cone function. The electroretinogram obtained under anesthesia showed normal light-adapted response. X-rays of the skull and facial bones were consistent with microcephaly, hypoplasia of the maxilla, and hypertelorism. Chromosome analysis on leukocytes, using a Giemsa banding technique, revealed a karyotype 46, XX, $4p^-$.

The parents and the two siblings were phenotypically normal. The parents had normal chromosomes when examined by Giemsa banding.

Case 2—A white male infant weighing 2,300 g was born to a 28-year-old, gravida 2, para 1 mother at 35 weeks' gestation in October 1959. At birth he had hyporeflexia and hypotonia. Another examination revealed that he had microcephaly, low-set ears, synophrys, malar hypoplasia, high arched palate, a depressed area from an occipital scalp defect, and profound retardation. He has lived in an institution for the retarded for most of his life. An electroencephalogram showed diffuse cortical damage. A chromosome karyotype by a Giemsa banding technique showed 46, XY, $4p^-$.

An ocular examination at age 18 years (Fig. 4) showed the patient could briefly fixate on a light and follow, but the responses were inconsistent and unsustained. Blepharoptosis, moderate exophthalmos, and antimongoloid palpebral fissures were present bilaterally. There was hypertelorism with an interpupillary distance of 67 mm. The inner canthal distance was 30 mm, and the outer canthal distance was 85 mm. The Schirmer test No. 1 was normal bilaterally. Schiøtz intraocular pressures were 15.6 mm Hg bilaterally. Both clear corneas measured 10 mm. Both pupils were ectopic, being displaced



Fig. 4 (Wilcox, Bercovitch, and Howard). Case 2, age 18 years.

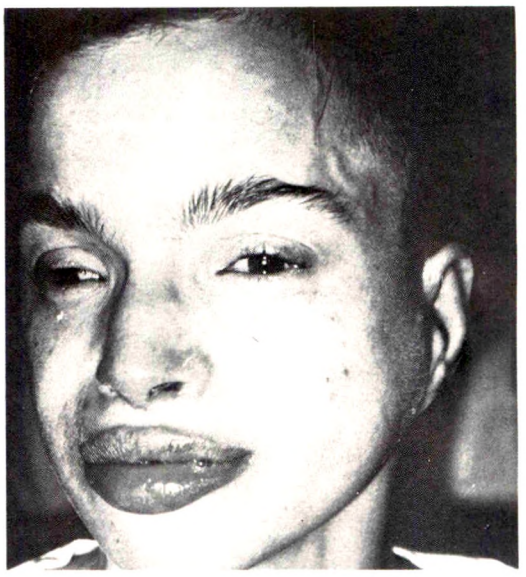


Fig. 5 (Wilcox, Bercovitch, and Howard). Case 3, age 23 years.

slightly superior and nasal. Iris crypts were absent, but the stroma was not atrophic. On gonioscopy, the iridocorneal angle was open to the posterior trabeculum for 360 degrees; scattered iris processes inserted into Schwalbe's line bilaterally. The lens and vitreous were clear. A crescent-shaped, peripapillary, slate-gray pigmentation about one disk diameter in width was present on the temporal disk margin of each eye; all retinal vessels emerged on the nasal rim of the disk; a thick veil of grayish glial tissue obscured the nasal margins of the disk. Foveal reflexes were present bilaterally.

Case 3—A white male weighing 2,100 g was born by cesarean section to a 27-year-old, gravida 5, para 4 mother at 36 weeks' gestation. The physical findings included a flat hemangioma of the back, hypospadias, bilateral inguinal hernias (subsequently surgically repaired), microcephaly, diastasis recti, and lumbar scoliosis. The patient has had ten episodes of pneumonia and generalized seizures, controlled with phenytoin. At present he is bedridden, profoundly retarded, and lives in an institution for the retarded. Chromosomal analysis by a Giemsa banding technique revealed 46, XY, $4p^-$.

An ocular examination at age 23 years (Fig. 5), revealed that he had synophrys and bilateral blepharoptosis. There was apparent hypertelorism, and 30 prism diopters of exotropia. The interpupillary distance was 50 mm. The inner and outer canthal distances measured 30 mm and 78 mm, respectively. The ocular motility was unrestricted. He had a brief, unsustained fixation of light, but failed to follow, and there was no response to an optokinetic stimulus. Refraction with cyclopentolate HCl was approximately −5.50 - 0.75 axis cyl 180 in each eye. The Schirmer test No. 1 was normal in both eyes. The intraocular pressure was 17.6 mm Hg in the right eye and 15 mm Hg in the left eye. The corneal diameter measured 9.5 mm in each eye, and appeared to be reduced by mild scleralization. Pupils were displaced slightly nasally, and the pupillary response was sluggish in both eyes. Gonioscopy revealed that the iridocorneal angles were open to the scleral spur for 360 degrees, and iris processes were absent. The lens and vitreous were clear. Both optic nerves had extreme cupping, a cup:disk ratio of about 0.7, and pallor with atrophy extending to the rim temporally. The retinal arteries and veins were tortuous.

Discussion

The prominent clinical features[12–14] in the chromosome deletion $4p^-$ syndrome include low birth weight, profound mental retardation, microcephaly, and a relatively characteristic physiogonomy of carp-like mouth, broad-based nose, low-set ears, hypertelorism, and antimon-

goloid palpebral fissures. Many of the affected individuals will also have a midline scalp defect, preauricular sinus or dimples, midline oropharyngeal defects (cleft lip or palate, nose abnormalities, micrognathia), genito-urinary abnormalities in the males, congenital heart disease (atrial or ventricular septal defects), and a sacral sinus.[15–17] Some of these features are also common to the other B-group deletion syndrome $5p^-$.[11,18,19] The clinical features of both are listed in Table 1.

Ocular abnormalities appear to be common in the $4p^-$ syndrome. An antimongoloid eyelid fissure, blepharoptosis, and exotropia are readily apparent on examination of the eyes and were noted in all of our cases. With exotropia, the eyes may give the appearance of hypertelorism; however, a true increased bony separation of the inner orbital walls has been measured for at least one patient (Case 1). Of interest in our cases were the anterior segment abnormalities, such as mild microcornea (9 to 10 mm), which may be partially explained by the tendency for scleralization of the cornea at the corneoscleral limbus. All of our patients had ectopic pupils (Fig. 3). Additionally, one patient (Case 1) had the first reported Rieger's anomaly associated with the $4p^-$ syndrome. A prominent appearance of the globes, abnormal eyelid retraction, nasolacrimal obstruction, iris processes in the posterior embryoxon, Peters' anomaly,

TABLE 1

CLINICAL CHARACTERISTICS IN $4P^-$ AND $5P^-$

	Common Features	Comments
	Low birth weight	Significantly less in $4p^-$ than $5p^-$, that is, in one series [11] mean birth weight 1866 g ($4p^-$) v 2650 g
	Hypotonia	
	Mental and developmental retardation	Prenatal onset in both, but more profound in $4p^-$
	Microcephaly	
	Apparent hypertelorism	
	Micrognathia	
	DIFFERENTIATING FEATURES	
	Wolf-Hirschhorn $4p^-$	Cri-du-chat $5p^-$
Mouth	Carp-like	Round
Craniofacial defects	More pronounced with asymmetry of head	Less frequent, less severe
Cleft palate/lip	About 2/3 of cases	Rare
Midline scalp defects	between 10-50%	not reported
Abnormal nose	Beaked in over 80%	
Hypertelorism	apparent hypertelorism in some cases due to microcephaly	Radiologically confirmed in many cases
Central nervous system	High incidence convulsions	Low incidence convulsions
Cry	Not distinctive; one case of cat cry in $4p^-$ doubtful [15,17]	Typical cat cry
Ears	Pre-auricular sinus	Not found, occasional pre-auricular tags
	Extremely undifferentiated simple ear	More differentiation and structure to ear
Genito-urinary	Hypospadias in males	Not reported
Cardiac	Septal defects frequent	Various congenital defects

iridocorneal angle, Brushfield spots, colobomas of the iris and choroid, optic nerve colobomas, and various refractive errors have also been recorded with the $4p^-$ chromosome abnormality.[20,21]

Considerable overlap is evident between the ocular findings in patients with the chromosome deletions $4p^-$ and $5p^-$ [22–25] (Table 2). In contrast to reports of individuals with $5p^-$ along with abnormal Schirmer test results, all patients with $4p^-$ including ours have had no dry eye problems. Clinically, the occurrence of blepharoptosis, anterior segment abnormalities, and normal tearing in individuals with $4p^-$ should help distinguish between the two syndromes. However, the correct diagnosis must always be confirmed in any patient with a chromosome determination, by using a banding technique. The cri-du-chat anomaly has occurred with Goldenhar[26] and possibly Ehlers-Danlos[27] syndromes, but the Wolf-Hirschhorn syndrome has not been reported with any other systemic syndrome.

At present, it is not possible to specify the individual genes deficient in the $4p^-$ syndrome, and thereby to correlate specific ocular abnormalities with specific gene abnormalities. The deletion in $4p^-$ may be interstitial or involve the loss of a terminal segment.[7,10] Examination of the chromosomes of the parents of these affected children is important because one of the parents often has a balanced translocation with a $5p^-$ chromosome, and the deleted segment fused to another chromosome. The parent would then be capable of producing another chromosomally abnormal child.[28] This does not now appear to be a factor for the $4p^-$ aberration.

As children with $4p^-$ syndrome have had increased medical care, their life span has been increased. As additional cases of the $4p^-$ syndrome are reported, the full spectrum of ocular abnormalities occurring in this syndrome will be evident.

TABLE 2

OCULAR FINDINGS IN THE $4p^-$ SYNDROME*

	Case 1	Case 2	Case 3	Previous Cases of $4p^-$	Previous Cases of $5p^-$
Hypertelorism	+	+	+	++++	+++
Antimongoloid fissures	+	+	+	++++	+++
Blepharoptosis	+	+	+	+++	±
Exotropia 30-40Δ	+	+	+	++++	++
Anterior segment anomalies	+ (Rieger's)	+	0	+++	±
Disk abnormalities	+	+	+	+	+
Microcornea ≦ 10 mm with scleralized cornea	9 mm	10 mm	9.5 mm	Part of anterior segment anomalies	0
Interpupillary distances	52 mm	67 mm	50 mm	—	—
Pupil/iris abnormalities (Ectopic pupils)	+	+	+	Part of anterior segment anomalies	0
Synophrys	0	+	+	+++	+++
Refraction	Mild hyperopia	Plano	Mild myopia	Variable	Variable
Deficient tears (Abnormal Schirmer)	0	0	0	0	++
Nasolacrimal obstruction	0	0	0	+	0
Iris/choroid colobomas	0	0	0	++	0

*+designates present; ++++, present in vast majority of cases; ± rare; 0, unreported.

SUMMARY

By using the Giemsa banding technique we identified three patients with chromosome deletion 4p⁻. All had anterior segment anomalies, exotropia, blepharoptosis, antimongoloid palpebral fissures, hypertelorism, and disk abnormalities. One patient (Case 1) had Rieger's anomaly.

Some clinical features in patients with 4p⁻ are similar to those in patients with chromosome deletion 5p⁻, cri-du-chat syndrome, although 4p⁻ individuals do not have the distinctive cry. The ocular features which distinguish 4p⁻ from other deletions include normal tearing, some degree of blepharoptosis, and the preponderance of anterior segment signs.

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NOTES, CASES AND INSTRUMENTS

NEW FLAT AIR INJECTION CANNULA

EDGAR A. RAININ, M.D.
Walnut Creek, California

Current 30-gauge air cannulas are used to instill and extract air and various intraocular medications such as acetylcholine, carbachol, and balanced salt solution into and out of the anterior chamber during intraocular surgery. Maintenance of the anterior chamber during intraocular lens insertion and anchoring has proven to be of extreme importance in protecting the corneal endothelium from contact with the polymethylmethacrylate surface of the intraocular lens.[1] With the short, 4-mm round, 30-gauge air cannulas, Descemet's membrane is often detached at the wound edge by the sharp tip of the cannula as it enters the anterior chamber. It has proven difficult to place air over the smaller diameter intraocular lenses because of the short length of the cannula. This may result in air being inadvertently instilled beneath the intraocular lens, forcing it against the endothelium.

To prevent these problems I have designed a 6-mm long, 30-gauge air cannula*, that has been modified by flattening the first 3 mm so that the opening is oval rather than round (Fig. 1). Additionally, the tip of the cannula is polished so that no sharp edges contact ocular tissues. The flat contour of this cannula protects against anterior chamber shallowing, and the extra length allows the tip to be inserted over the anterior surface of the lens easily for instillation of air into the anterior chamber (Fig. 2). The chances of Descemet's membrane stripping are greatly reduced by the polished, flattened tip of the instrument.

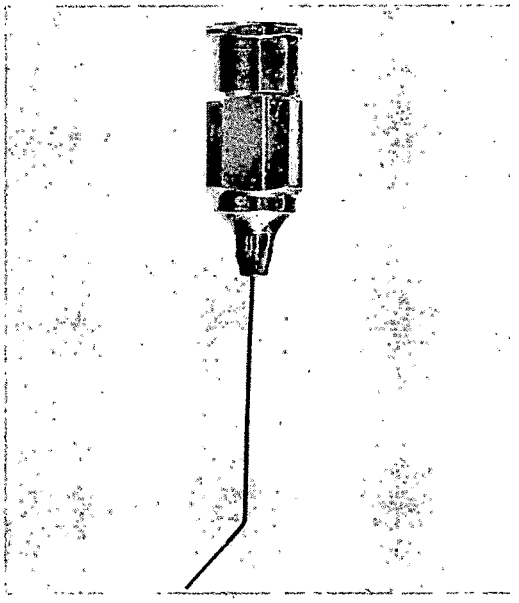


Fig. 1 (Rainin). Flattened, 30-gauge air cannula.

I have used this instrument during intraocular surgery for the past two years and have found it useful in reducing the incidence of Descemet's membrane de-

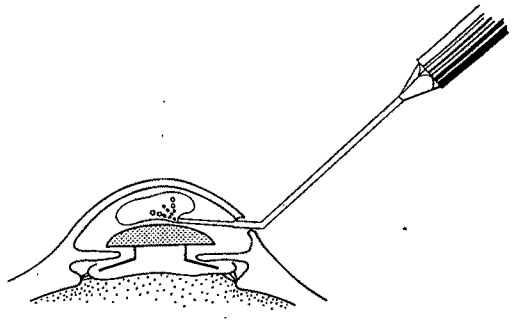


Fig. 2 (Rainin). The flattened long tip of the cannula allows air injection over the intraocular lens, protecting the endothelium from the lens.

From the Department of Ophthalmology, University of California, Davis, California.
Reprint requests to Edgar A. Rainin, M.D., 2021 Ygnacio Valley Rd., Walnut Creek, CA 94598.

*Available from Katena Products, Inc., 10 Great Meadow Lane, East Hanover, NJ 07936.

tachments and loss of the anterior chamber during intraocular lens insertion.

SUMMARY

I developed a 6-mm long, flattened, 30-gauge air cannula with a polished tip for instillation and extraction of air and fluids from the anterior chamber during intraocular surgery. The polished flattened tip prevents Descemet's membrane detachments and the extra length allows easy instillation of air over an intraocular lens.

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MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

IOWA EYE ASSOCIATION 1978 ANNUAL MEETING

The Iowa Eye Association meeting took place in Iowa City from June 1 to 3, 1978. More than 35 alumni, faculty, fellows, and residents of the Department of Ophthalmology participated in the meeting. Norman Byer, clinical professor of ophthalmology at the University of California was the invited guest. His presentations were entitled, "Peripheral retina - Friend or foe? 1. Retinoschisis; and 2. Lattice degeneration." The program covered a broad range of topics based on clinical and laboratory studies. Some highlights of the program were as follows:

RETINA

Thomas Burton demonstrated in a retrospective study of retinal detachment patients that the duration of macular detachment has a direct bearing on final visual acuity. The sooner the macula is reattached the better the visual prognosis.

In a review of 196 cases of retinal dialysis, Victor Zion noted that the vast majority were associated with a history of trauma and that clinically there is little to differentiate cases associated with a history of trauma from those without such a history. Any unilateral dialysis other than inferotemporal is "pathognomonic" of trauma. The extremely high incidence of trauma in patients with inferotemporal dialysis (50% in this study), as compared with the general detachment population, makes it likely that many of these dialyses were also traumatic even though the patients denied such a history.

Transient central retinal artery occlusion in monkeys lasting 15 minutes to 4½ hours was described by Sohan Hayreh, Hansjoerg Kolder, Wayne March, and Thomas Weingeist. No ophthalmoscopic, angiographic, electrophysiologic, or morphologic alterations were noted three months after central retinal artery occlusion lasting up to 90 minutes. Central retinal artery occlusion of 105 minutes or longer always produced marked ophthalmoscopic and morphologic damage in the retina and optic nerve and absence of the visual-evoked response. The b-wave of the electroretinogram showed irreversible changes only after ischemia of longer than 2½ hours.

Louis Lobes described pupillary abnormalities that occurred in diabetic patients after "panretinal" photocoagulation. The patients had a light-near dissociation (better near than light reaction), segmental palsy of the iris sphincter, impaired accommodation, and cholinergic supersensitivity just as in Adie's syndrome. This acquired condition is assumed to originate from chorioretinal laser burns involving the short ciliary nerves, rather than damage of the iris muscles.

GLAUCOMA

Charles Phelps and Nour-Iddin Arafat discussed the results of a randomized double-masked clinical trial in which the effectiveness and safety of timolol, a beta-adrenergic blocker, and epinephrine were compared in lowering intraocular pressure of patients with ocular hypertension and primary open-angle glaucoma. Timolol appears to be more effective than epinephrine and showed no evidence of tachyphylaxis when used twice daily during at least a four-month period. No important systemic or ocular side effects were noted with timolol. Since timolol does not constrict the pupil or induce

accommodative spasm, it may be particularly useful in young patients. Furthermore, its apparent safety may mean that it can be used in the management of ocular hypertension without evidence of optic nerve damage. Further clinical trials are needed.

STRABISMUS

David Werner, Leslie Weingeist Lennarson, and William Scott found that the Jensen procedure was effective in treating patients with severe lateral rectus palsy (<40% normal saccadic function). Postoperatively all patients had improved saccadic function, 12 of 13 showed a functional area of binocular single vision and 11 of 13 had aligned eyes with good head position. Patients with greater than 75 prism diopters of deviation had a medial rectus recession of more than 6.5 mm, whereas those with less than 75 prism diopters of deviation had recessions of between 4.0 and 6.5 mm.

Thomas Smith, Paul and Walter Remijan, and Hansjoerg Kolder have developed a new, patented device for testing retinal function in the presence of opacities of the media. The outstanding features of this "laser acuity" instrument include (1) precise calibration, (2) variable field (0.5 to 15 degrees), (3) high contrast pattern, (4) variable intensity, (5) ease of operation without optical adjustment, and (6) small size. Initial testing in amblyopic patients has demonstrated that "acuity" is better with small field sizes using the holographic phase grating pattern than is obtainable clinically. After increasing the field size "laser acuity" and Snellen acuity correspond better in amblyopic patients. Variation in "laser acuity" with field size may aid in the diagnosis of amblyopia particularly in the presence of opaque media.

The next Iowa Eye Association meeting is scheduled for June 7-9, 1979.

THOMAS A. WEINGEIST

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SCIENTIFIC REFEREES AND THE AMERICAN JOURNAL OF OPHTHALMOLOGY

Preceding the index section of this issue are the names of some 100 plus ophthalmologists, physicians, and scientists who have reviewed manuscripts submitted for publication in 1978. These individuals work anonymously and contribute their time and talent freely to assure the excellence and accuracy of THE JOURNAL. Their contribution to medical education is enormous. Thus, please turn to the index and note their names. If you are acquaintted with any of them, please thank them for their contributions to ophthalmology and to the readers of THE JOURNAL.

I thought of scientific referees recently when a reader complained that although the Center for Communicable Disease Control stated in 1973 that bacitracin was not indicated for prophylaxis of ophthalmia neonatorum, it was listed as the agent of choice in the treatment of gonorrheal ophthalmia in both the transactions of an ophthalmic society and a recent textbook. The problem is of course that transactions and textbooks have no scientific referees, and thus, their statements have not met the acid test of critical review.

The scientific referees perform a number of chores in reviewing a manuscript. They assist in determining the originality of a paper and whether the material has been published previously. They examine the accuracy of statistics, the design of a study, and the legitimacy of conclusions. They direct attention to tables, illustrations, and references. They indicate the strengths and weaknesses in the structure of a paper. Indeed, I know of no better way of having a first-class critique of a paper than by submitting it for consideration to a referred journal.

What then of the nonrefereed sources? Conclusions are difficult to make, but basically one must depend on the ability of the author, the purpose of the journal, and the critical reputation of the editor. Material such as philosophical or reflective pieces and reviews may not be suitable for refereed journals because they do not provide original material. Some non-

refereed journals are notorious for publishing ideas or procedures that have been rejected by refereed journals.

The scientific review is but one of the three review processes carried on at THE JOURNAL. An internal editorial review is directed toward the suitability of the paper for publication, based on the stylistic requirements unique to THE JOURNAL. These stylistic requirements are published periodically in THE JOURNAL as Instructions to Authors. They include instructions for preparation of references, legends, and figures, as well as mechanical preparation of the text.

The third process is directed toward the suitability of the paper for publication based on material in press and that which has recently published not only in THE JOURNAL, but in other publications. This process is carried out by the Editorial Board and the Editor-in-Chief. A current awareness of what has been done is maintained through regular reading of perhaps 20 standard journals: the Archives of Ophthalmology, Investigative Ophthalmology and Visual Science, Survey of Ophthalmology, Canadian Journal of Ophthalmology, Japanese Journal of Ophthalmology, Klinische Monatsblätter für Augenheilkunde, Acta Ophthalmologica, Ophthalmologica, and the transactions of various societies—the American Academy, the American Ophthalmological Society, and the ophthalmological societies of the United Kingdom and France. The Annals of Internal Medicine, New England Journal of Medicine, Lancet, British Medical Journal, Science, and Nature are culled. Other journals are reviewed in medical libraries. Thus, even though a paper may be original to THE JOURNAL, the Editorial Board tends not to use it if there seems to be a plethora of published articles on the same topic.

Even with the delicate review mechanism of THE JOURNAL, however, articles slip by that are published when they should not have been, published prematurely, or rejected instead of being accepted. Sometimes the scientific referees disagree and the editorial decision made is contrary to the views of at least one scientific referee. Occasionally, a paper is accepted for publication in which the author's strong views on retaining participles, passive voice, split infinitives, or medical jargon are not discovered until the editing process. Despite these failings, however, each issue of THE JOURNAL constitutes the work not only of the some 100 scientific referees and the Editorial Board members whose names are published, but a devoted group of talented workers anxious to provide the JOURNAL readers with the best possible publication.

FRANK W. NEWELL

OBITUARY

V. Everett Kinsey, Ph.D.
1909-1978

V. Everett Kinsey, a leading ophthalmic researcher of this century, died July 28, 1978, in Harper Hospital, Detroit, Michigan, after a stroke suffered earlier. A pioneer of research ophthalmology in its formative years, he made major contributions to our understanding of the transparency of the cornea, the secretion of aqueous humor, the pathogenesis of retrolental fibroplasia, and the metabolism of the lens.

He was born in Pittsburgh in 1909 and received the bachelor of science degree from the University of Pittsburgh in 1931. He then assisted the mathematical biologist Dr. Nicholas Rashevsky in biophysical research at the research laboratory of the Westinghouse Electric Company, and became interested in the effects of x-rays on living tissue. In 1935, he obtained a Ph.D. degree in zoology from the University of Pittsburgh where he studied the biologic effects of x-rays on glutathione, phosphotase, and esterase. The following year he studied the effects of short-wave

radiations at the Cancer Research Laboratory at the University of Pennsylvania, and in 1937 and 1938 he worked as a research biochemist at the Sharp and Dohme Biological Laboratories. He investigated methods of purifying antitoxins. In 1938, he became a research associate in the Department of Ophthalmology at the University of Pittsburgh.

In 1940, he joined the staff of the Howe Laboratory of Ophthalmology of the Harvard Medical School as an assistant in ophthalmic research. His initial studies on the cornea with David Cogan led to accurate delineation of the movement of water through the cornea and much of our early information on the deturgescent mechanism. For these studies, he shared with Dr. Cogan the Warren triennial award of Massachusetts General Hospital. In 1942, he began studies with W. Morton Grant on the kinetics of intraocular fluid transport, which led to our present theories of aqueous humor secretion and the nature of the primary aqueous humor secreted into the posterior chamber. Ocular injuries to arc welders during World War II led to the study of ultraviolet keratitis. Additional studies concerned the actions of mustard gas on the eye.

From 1946 through 1950 he was director of research on retrolental fibroplasia at the Massachusetts Eye and Ear Infirmary. He subsequently headed a collaborative group that studied the role of oxygen in this disorder. For this work he received the Modern Medicine Distinguished Award and the Lasker Award. In 1950 Dr. Kinsey turned his attention to the lens. He developed a method to maintain the lens in vitro and demonstrated that the epithelium was responsible for the transport function in this lens.

Throughout his life he had tremendous enthusiasm and was responsible for stimulating many individuals to enter ophthalmology. He was unfailingly generous and collaborated with a number of distinguished investigators, many of whom he had initially directed. From 1950 to 1968 he was assistant director of the Kresge Eye Institute of Wayne State University and professor of ophthalmic chemistry. In 1968, he went to Oakland University as the first director of the Institute of Biological Sciences, where he became director emeritus in 1975.

In addition to his vision research, Dr. Kinsey was active in organizational ophthalmology. He was adviser to the National Society for the Prevention of Blindness on retrolental fibroplasia; he was chairman of the committee on this topic from 1968 until his death. He served as a member of the Society's Committee on Basic and Clinical Research since 1949. He served as a trustee and chairman of the Association for Research in Ophthalmology (now ARVO), as a member of the Sensory Disease Study Section of the United States Public Health Service of the National Institutes of Health, and subsequently on the Council of the National Institute for Neurologic Diseases and Blindness and the Council of the National Eye Institute. He was the first chairman of the National Eye Institute Board of Scientific Counselors. He served on the editorial boards of the Archives of Ophthalmology and Experimental Eye Research. He served as chairman of the Scientific Advisory Board of the National Foundation for Eye Research and as a member of the Scientific Advisory Board of the National Council for the Prevention of Blindness (Fight for Sight!). He was an early advocate of scientists working with clinicians to solve medical problems. He was an honorary member of the New England and the Detroit ophthalmological societies.

Dr. Kinsey received the Proctor Medal Award of the Association for Research in Ophthalmology in 1952. At that time he expressed the need for tenured positions for full-time investigators in ophthalmol-

ogy, adequate laboratory space for experimental studies, and adequate funding. His philosophy was expressed in his remarks made at the acceptance of the Proctor Medal Award (Am. J. Ophthalmol. 36:7, 1953), and earlier in Science (105: 373, 1947).

Science was but one of his interests and he brought leadership and devotion to whatever activity he undertook. He was a director of the Detroit opera theater. He became interested in boating, and became an instructor in a powerboat squadron. He was an analytic thinker, and nothing was more pleasant than to review a day's scientific program with Everett commenting on what should have been done, how data could have been interpreted differently, and the new problems encountered.

Everett Kinsey's death reflects the end of an early era in ophthalmology. As we consider the many laboratories now devoted to ophthalmology, the publications that serve to disseminate their results, and devoted investigators in this field, we must appreciate that he was a far-sighted pioneer who did much to bring them about through his example and urging.

Dr. Kinsey is survived by his wife Irene whom he married in 1935.

FRANK W. NEWELL

CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper, with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

Intraocular Lens Implant—Visual Success, Psychological Complication

Editor:

The following vignette of a visually successful but psychologically disastrous intraocular lens procedure may be of interest.

An 82-year-old woman slowly lost vision because of bilateral cataracts over a 20-year period. Vision decreased to R.E.: 6/30 (20/100) and L.E.: 6/120 (20/400). A cataract extraction with a Copeland intraocular lens implantation was carried out. Postoperatively vision was improved to L.E.: 6/9 (20/30).

The patient is now incensed with the image of herself in the mirror. She brought in a picture taken at age 21 and stated, "This is what I looked like before the cataract extraction. You have made my face look like a baked apple." She is unhappy with her visual acuity and unhappy with her physical appearance and emphasizes this with threats of litigation involving the surgeon and the anesthetist. ("If the surgery wasn't the cause of the wrinkles it must have been the poison gases.") We have been unable to reconcile her to her better vision and aging appearance.

THOMAS D. DICKINSON, M.D.
Sarasota, Florida

Cell-Mediated Immunity After Retinal Detachment

Editor:

In the article, "Cell-mediated immunity after retinal detachment as determined by lymphocyte stimulation" (Am. J. Ophthalmol. 86:216, 1978), C. J. J. Brinkman and R. M. Broekhuyse concluded that cell-mediated immunity against retinal antigens occurs after retinal detachment and may be of primary importance in the understanding of biological events following retinal detachment. This specific blast transformation phenomenon is a sensitive test, but to reach an adequate conclusion concerning possible autoimmune phenomenon in retinal detachment more essential information concerning the results and experimental design are required.[1,2]

An age- and sex-matched population

not suffering from retinal detachment, but having other ocular disorders, must be included. Normal controls are required too and they must also be age- and sex-matched. Testing must be carried out at the same time, in the same conditions, in the matched manner, and preferably in a masked method. Conclusions on specificity based on the sole response to one antigen without proper controls can be erroneous and may be misleading. The more than 20-fold difference in the magnitude of the response toward phytohemagglutinin-P raises many questions concerning the validity of the conclusions concerning the "specific" stimulation by ocular antigens.[3]

Although there is a possibility that some autoimmunity against retinal antigens may develop after retinal detachment, the results presented in the study are insufficient and cannot be considered as providing an indication for the development of specific cellular immunity against retinal antigens after retinal detachment.

Although Henley, Okas, and Leopold[4] suggested some indication of cellular immunity toward ocular tissues, these have not been confirmed or repeated. In my own studies following rigid criteria for the selection of the patients and controls, and performing the test in a matched and masked manner, no specific cellular immune responses toward retinal or other ocular antigens were observed in a group of 16 patients with retinal separations of various causes.

DAVID BENEZRA, M.D.
Jerusalem, Israel

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2. BenEzra, D., Gery, I., and Davies, A. M.: Transformation of rabbit lymphocytes by specific antigens. Proc. Soc. Biol. Med. 125:1305, 1967.

3. Ehrenfeld, E. N., Klein, E., and BenEzra, D.: Human thyroglobulin and thyroid extracts as specific stimulators of sensitized lymphocytes. J. Clin. Endocrinol. Metabol. 32:115, 1971.

4. Henley, W. L., Okas, S., and Leopold, I. H.: Leucocyte migration inhibition by choroid and retina in retinal detachment. Ophthalmic Res. 7:129, 1975.

Reply

Editor:

Concerning the adequacy of our controls, patients suffering from other accompanying disorders must be included as a control group. This certainly is an important point for further studies. However, Table 1 in our article shows that of ten patients with retinal detachment but without accompanying ocular disorders five reacted positively with retinal antigens. This indicates, at least in these patients, that retinal detachment is related to an activation of the immune system to retinal antigens. In view of the progressive activation of the cellular immune system, retinal detachment is the likely initiator of this activation. Furthermore, the patients suffering from retinal detachment for less than about one month may be considered as "controls" for the group of patients suffering from retinal detachment for more than one month (refer to Table 3).

In view of the techniques used it is important that patients and healthy subjects were tested at the same time with the same batch of antigens. The separation of the patients according to the duration of the detachment was made after having tested them all. A number of patients and healthy subjects were tested twice with negligible differences in response.

Our results show that patients suffering from prolonged retinal detachment have lymphocytes sensitized to retinal antigens. Immunization of animals with autologous retinal extracts results in chorioretinitis,[1] which strongly suggests that retina contains tissue specific antigens. The possibility exists, however, that the

response of the patients suffering from prolonged retinal detachment would have a limited specificity. This has to be studied further.

Concerning the results, a considerable variation in phytohemagglutinin stimulation has been found by many other investigators[2–4] and is difficult to explain. However, patients demonstrating a relatively low phytohemagglutinin stimulation may still react positively with retinal extracts (Table 1, Nos. 5, 6, 25, and 28). Hence, it is hard to state that a mitogen (phytohemagglutinin) response is indicative for an antigen response. One of the main reasons we incubated the lymphocytes with phytohemagglutinin was to test their viability. We stated that an S.I. $\geqq 20$ with tissue antigens is seldom encountered. This is indeed the case in our group of patients using human soluble retinal antigens. However, when one uses animal tissues as a source of antigens there is always the problem of histoincompatibility, which might be the cause of an aspecific stimulation of the lymphocytes. We have found this with many other tissues of the bovine eye. Other investigators found high stimulation indices with lymphocytes of patients suffering from rheumatoid arthritis after incubation with human collagen.[5]

Some reasons for the negative results found by Dr. BenEzra (which are difficult to judge, because they have not been published) may be as follows: technical aspects of the lymphocyte stimulation test including the counting system, the source of antigen (isolated from frozen or fresh eyes), the duration of the detachment.

C. J. J. BRINKMAN, M.SC.
R. M. BROEKHUYSE, PH.D.
Nijmegen, The Netherlands

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Postcyclocryotherapy Complications

Editor:

The recent report, "Cyclocryotherapy in neovascular glaucoma" (Am. J. Ophthalmol. 86:24, 1978), by T. Krupin, K. B. Mitchell, and B. Becker showed a high incidence of serious complications following cyclocryotherapy, including phthisis bulbi in 17 eyes. A freeze-thaw-refreeze technique was used in 14 eyes in the series. This technique has been previously reported to cause phthisis bulbi.[1]

Although the authors state that " . . . the development of phthisis bulbi (was) related neither to the number of cryogenic lesions nor to the manner of their application," further details on the outcome of eyes treated with freeze-thaw-refreeze would be welcome in light of the problems previously reported with this technique.

THOMAS HANSCOM, M.D.
Durham, North Carolina
HERBERT E. KAUFMAN, M.D.
New Orleans, Louisiana

REFERENCE

1. West, C. E., Wood, T. O., and Kaufman, H. E.: Cyclocryotherapy for glaucoma pre- or postpenetrating keratoplasty. Am. J. Ophthalmol. 76:435, 1973.

Reply

Editor:

We appreciate the interest shown by Drs. Hanscom and Kaufman regarding our recent article. In our study phthisis

bulbi occurred in 17 eyes. A freeze-thaw-refreeze technique was performed on 14 eyes with four (28%) of these eyes developing phthisis bulbi. This complication occurred following a single freeze-thaw technique at —60° C in nine of 25 (36%) eyes, and at —80° C in four of 15 (27%) eyes. Unfortunately, many factors including size and location of the cryogenic lesion, duration and temperature of the freezing, and extent of the eye treated account for some of the variable effects as well as complications of cyclocryotherapy.

THEODORE KRUPIN, M.D.
KENNETH B. MITCHELL, M.D.
BERNARD BECKER, M.D.
St. Louis, Missouri

HLA Antigens in Cogan's Syndrome

Editor:

I was interested to read the article, "The HLA antigens in Cogan's syndrome" (Am. J. Ophthalmol. 86:314, 1978), by M. I. Kaiser-Kupfer, K. K. Mittal, L. A. DelValle, and B. F. Haynes, and the article in the New England Journal of Medicine,[1] presenting their negative study on HLA typing in Cogan's syndrome. We studied immunologic function in a group of these patients in 1974, and among a large number of immunologic tests performed, we reported that three of four patients typed in a masked manner by an independent typing laboratory had a positive cytotoxicity test for a tentative workshop antigen, HLA-W17.[2] Because of the small numbers tested we deliberately did not make any inferences from these data. Using newer, better defined antigens not available at that time, Kaiser-Kupfer and associates have been unable to demonstrate the presence of a definitive B17 antigen in patients with Cogan's syndrome. We agree with their conclusions; we had also stated in our previous article that too few patients were typed to draw significant conclusions in Cogan's syndrome.

DEVRON H. CHAR, M.D.
San Francisco, California

Reply

Editor:

Dr. Char comments on an important point that was stressed in our paper, that is, the cautious interpretation of data derived from a small sample. We would like to reiterate that the importance of our report lies in clearly demonstrating an absence of B17 antigen in nine of ten patients with Cogan's syndrome. These nine patients included the four patients studied by Char, Cogan, and Sullivan.[2]

MURIEL I. KAISER-KUPFER, M.D.
KAMAL K. MITTAL, PH.D.
Bethesda, Maryland

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2. Char, D. H., Cogan, D. G., and Sullivan, W. R.: Immunologic study of nonsyphilitic interstitial keratitis with vestibuloauditory symptoms. Am. J. Ophthalmol. 80:491, 1975.

Levator Palpebrae Superioris Muscle Insertion

Editor:

In the article, "Experimental and clinical data on the insertion of the levator palpebrae superioris muscle" (Am. J. Ophthalmol. 85:792, 1978), by J. R. O. Collins, C. Beard, and I. Wood, the authors state that "the aponeurosis was found to insert between the orbicularis muscle bundles beginning approximately at the level of the upper border of the tarsus in the area of the skin crease and onto the lower half of the anterior surface of the tarsus". This perpetuates the old

concept that the aponeurosis has multiple insertions. Any insertion onto the lower half of the tarsal plate would mean a Horner blepharoptosis would be impossible unless that portion of the aponeurosis inserting into the lower half of the tarsal plate were corrugated horizontally to allow the lower half of the eyelid to droop when Müller's muscle is paralyzed or relaxed and it would have to corrugate even more with eyelid retraction. In 1962 (Br. J. Ophthalmol. 48:503, 1962), I stated that the aponeurosis has a single insertion into the palpebral fascia about midway between the orbital and eyelid margins (Figure). The upper part of the palpebral fascia, between the orbital margin and levator insertion, is relatively thick and commonly called the septum orbitale. The lower part of the fascia is thinner, more areolar in nature and forms the anterior face of the pretarsal space before it blends with the lower one fourth to one half of the tarsal plate. It does not look like the levator aponeurosis in appearance and consistency. From the palpebral fascia, septae extend between the arcuate bundles of the orbicularis oculi muscle and blend with the skin. The size and number of these septae vary in different races, which accounts for variations in the eyelid fold.

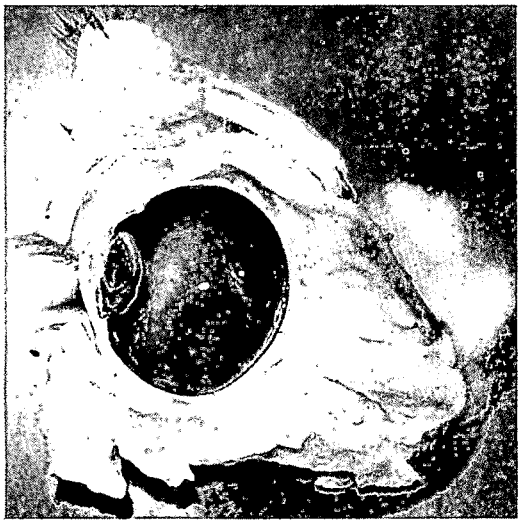


Figure (Epstein). A vertical section through the orbital contents. There has been no additional dissection except that small pledgets of wool have been inserted deep into the natural cleavages, which have been teased open between the aponeurosis and Müller's muscle; the pretarsal space; the bursal-like space between the aponeurosis, septum orbitale and orbital fat; the superior rectus and sclera; and the upper conjunctival fornix. The levator muscle gives rise to the aponeurosis which inserts into the palpebral fascia. The palpebral fascia can be traced from the orbital margin to its attachment to the lower part of the tarsal plate with the pretarsal space between them. Müller's muscle originates from the levator muscle beneath the aponeurosis and lies just deep to the conjunctiva. It inserts into the upper border of the tarsal plate.

In the past these septae have been dissected out as a layer of the aponeurosis that pierces the orbicularis to attach to the skin. This is an unusual anatomical concept and is equivalent to saying the tendons of the recti muscles pierce the sclera to become attached to the corneoscleral limbus. The concept of a corrugated block of tissue — pretarsal skin — orbicularis - oculi — muscle — and — palpebral — fascia, is more acceptable than a wrinkled aponeurosis. The tone of Müller's muscle as it passes from the under surface of the aponeurosis to the upper edge of the tarsal plate (I have also seen strands cross the pretarsal space blend with the lower part of the palpebral fascia) holds the lower half of the eyelid in its normal, drooping, or retracted position according to this tone. Textbooks have described this as one of the layers of the levator muscle. As it is a layer of smooth muscle, has a separate nerve supply, and a particular action of its own, it should be given the status of a separate muscle supplementing the action of the levator muscle in a particular way just as the lumbrical muscles originate from the deep flexor tendons and have a particular insertion and action of their own. I have suggested that it more descriptively be called the "cremaster tarsus."

The levator muscle is said to pull the eyelid upward. However, its insertion into the midpoint of the palpebral fascia pulls this point backward and with the attachment of the septum orbitale to the orbital margin as fulcrum, the eyelid folds on itself, deepening the eyelid crease, and the lash border is raised over the globe. With the eye enucleated the levator muscle merely pulls the eyelid backward into the socket (like a punka wallah) and the lash border barely elevates. I have long believed that one cause for blepharoptosis is an insertion of the aponeurosis above the midpoint of the palpebral fascia.

EDWARD EPSTEIN
Johannesburg, South Africa

Reply

Editor:

We are aware of Dr. Epstein's earlier article. His interpretation of the insertion of the levator aponeurosis is not shared by most anatomists. There have been too many gross dissections and histologic studies to allow for a change in the old concept that the aponeurosis has multiple insertions.

We believe that multiple insertions explain the mechanism of Horner's syndrome blepharoptosis far better than the theory Dr. Epstein describes in his letter. Surgeons who perform blepharoptosis surgery know there is a 2 to 3 mm stretch of the levator aponeurosis. The eyelid is probably held at a gross level by the tonus, contraction, and relaxation of the levator muscle. The fine adjustment is determined by the tonus of Müller's muscle overriding this levator action. If the levator aponeurosis was firm like the temporal muscle tendon, then Dr. Epstein's statement of the impossibility of Horner's blepharoptosis would be true. The levator aponeurosis, however, is not of a fixed length.

Any surgeon who dissects the eyelids carefully in blepharoptosis surgery knows that in about half of the cases the orbital septal attachment to the levator aponeurosis can be separated by blunt dissection. If this were a continuing membrane this would not be possible. We believe that at the junction of orbital septum and levator aponeurosis it is the aponeurosis that continues forward and not the palebral fascia.

Yours sincerely,

RICHARD COLLIN, F.R.C.S.
London, England
CROWELL BEARD, M.D.
San Jose, California

The Framingham Eye Study

Editor:

I was most interested in the article, "Prevalence of senile cataract, diabetic retinopathy, senile macular degeneration, and open-angle glaucoma in the Framingham Eye Study" (Am. J. Ophthalmol. 85:28, 1978), by M. M. Kini, H. M. Leibowitz, T. Colton, R. J. Nickerson, J. Ganley, and T. R. Dawber. However, I believe that the data quoted for the prevalence of lens opacities in the general population are remarkably low.

Slip-lamp examination with dilated pupils of a sample of 795 persons ages 40 to 74 years of a defined population of the Rhondda Fach in South Wales in 1964 and 1965 showed that cortical lens opacities were present in 43% of men in the age group 40 to 49 years, 57% of men in the age group 50 to 59 years, 77% of men in the age group 60 to 69 years, and 84% of those in the age group 70 to 74 years. The data for women were remarkably similar.

The cortical opacities were divided into 50% dots, 34% wedges and plaques, 20%

clubs, 5% fluid clefts and globules, and 4% posterior axial, more than one type being present in many instances.

I believe, therefore, that Kini and coworkers have concentrated on more marked lens opacities and their data seriously underestimate the presence of lens opacities in a defined population.

My data were published as part of an M.D. thesis for the University of Wales in 1965 and have been quoted in the Ciba Symposium, No. 19, "The Human Lens in Relation to Cataract" (Copenhagen, Elsevier, 1973, p. 283).

ROGER MCGUINNESS, M.D.
New South Wales, Australia

Helminthosporium Corneal Ulcers

Editor:

In the report, "*Helminthosporium* corneal ulcers" (Am. J. Ophthalmol. 85:666, 1978), by J. H. Krachmer, R. L. Anderson, P. S. Binder, G. O. Waring, J. J. Rowsey, and E. S. Meek, I noted several major errors. The fungus illustrated in Figure 3 isolated from the second case is *Drechslera* and not *Helminthosporium*. I would also suspect that the other cases were caused by this same organism. Based upon their figure, the case or cases can not possibly represent infections caused by *Helminthosporium*.

Helminthosporium is an extremely rare fungus, whereas *Drechslera* is not. Basically, *Helminthosporium* has a straight conidiophore, whereas *Drechslera* has one that is geniculate (bent-kneelike). Several cases have been caused by *Drechslera*. I feel the cases are noteworthy, but that the etiologic agents should be identified properly.

MICHAEL R. MCGINNIS, PH.D.
Chapel Hill, North Carolina

BOOK REVIEWS

Senile Retinoschisis. Morphological Relationship of the Formation of Spaces Within the Peripheral Retina to Senile Reitnoschisis and to Schisis Detachment. By Wolfgang Gottinger. Stuttgart, Georg Thieme Publishers, 1978. Clothbound, 60 pages, table of contents, index, 83 black and white figures, 7 tables.

In this monograph, the author describes his study of senile retinoschisis and related conditions in 315 pairs of human eyes obtained at autopsy. The study used gross observations, light microscopy, scanning electron microscopy, and transmission electron microscopy.

The author concludes that peripheral cystoid retinal degeneration forms the basis from which senile retinoschisis develops; columns between retinal microcysts rupture to produce the schisis cavity; Müller's cells participate in a reactive manner by producing basal membrane and collagenous microfibrils; and outer retinal layer breaks may be caused by shrinking of these collagenous microfibrils. Additionally, the author concludes that outer retinal layer breaks contribute to separation of the outer retinal layer from the adjacent pigment epithelium.

Although a more precise definition of retinoschis in terms of area of involvement would be helpful and the author considers senile retinoschisis as a single entity, this is an excellent study. It is particularly noteworthy for the gross eye stereophotographs, the scanning electron microscopy illustrations, and the extensive bibliography. I recommend this monograph to interested ophthalmologists and retinal research scientists.

BRADLEY R. STRAATSMA

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

Acta Ophthalmologica

LENTICONUS ANTERIOR AND ALPORT'S SYNDROME. Nielsen, C. E. (Dept. Neurosurgery, Aalborg Sygehus Syd, Aalborg, Denmark). Acta Ophthalmol. 56: 518, 1978.

Six patients, from five families, five males and one female, suffering from lenticonus anterior are presented. Furthermore, all suffered from chronic nephritis and nerve deafness and must be considered cases of Alport's syndrome. As all cases with lenticonus anterior which have been published within the last 13 years likewise were affected with nerve deafness and/or chronic nephritis, the assumption is submitted that lenticonus anterior exists exclusively as a part of Alport's syndrome. (2 figures, 2 tables, 63 references)—Authors' abstract

BINOCULAR INTERACTION STUDIED WITH VISUAL-EVOKED RESPONSES (VER) IN HUMANS WITH NORMAL OR IMPAIRED BINOCULAR VISION. Lennerstrand, G. (Dept. Ophthalmol., Univ. Hosp., Linköping, Sweden). Acta Ophthalmol. 56:628, 1978.

In an attempt to evaluate binocular functions in an objective manner, visual evoked responses (VER) were recorded in sixteen subjects, six with normal binocular functions and ten with various degrees of squint and binocular impairment. The two eyes were stimulated monocularly or dioptically with a polaroid checker board pattern viewed through rotating polaroid disks. The rate of pattern reversal was seven per sec for one eye and ten per sec for the other, allowing stimulus locked responses to be recorded from each eye individually, even during dioptic viewing. In normal subjects the VER of each eye to binocular stimulation were reduced to half or less of the monocular value. The reduction was much smaller in humans with impaired binocular vision, at least for the dominant eye. In stereoblind subjects the response of the dominant eye was the same for monocular and binocular stimulation. The VER changes might reflect binocular interaction in visual cortex neurons, which probably are binocular in normal subjects but driven only from one eye in stereoblind subjects. (4 figures, 1 table, 21 references)—Authors' abstract

American Journal of Surgical Pathology

SEBACEOUS CARCINOMA OF THE EYELID FOLLOWING RADIATION THERAPY. Lemos, L. B., Santa Cruz, D. J., and Baba, N. (Ohio State Univ. and Columbus Children's Hosp., Columbus, Ohio). Am. J. Surg. Path. 2:305, 1978.

A 12-year-old boy died from a sebaceous carcinoma originating from the eyelid. The carcinoma developed 11 years after curative radiation therapy for bilateral retinoblastoma. Sebaceous carcinomas associated with previous irradiation are uncommon, and only five such cases have been published. Three of the patients were treated for benign disorders and the two other cases followed radiation therapy for bilateral retinoblastoma. Second malignant neoplasms in patients with bilateral retinoblastoma are thought to be related to a genetically inherited predisposition to the development of second malignant tumors. Radiation therapy is claimed to be an inducing factor in many cases but malignant neoplasms are also found in areas distant from the portals of irradiation as well as in patients not irradiated. Most of the secondary tumors were sarcomas, and usually osteogenic sarcomas: (4 figures, 1 table, 31 references)—Authors' abstract

Archives of Ophthalmology

FLUORESCEIN IRIS ANGIOGRAPHY. Hayreh, S. S., and Scott, W. E. (Dept. Ophthalmol., Univ. of Iowa, Iowa City, Iowa). Arch. Ophthalmol. 96:1390, 1978.

Iris circulation was investigated by fluorescein iris angiography in 33 human eyes before and after tenotomy of one or more recti for correction of strabismus. Tenotomy of one or both horizontal recti produced no appreciable circulatory disturbance in the iris, but tenoto-

my of superior or inferior rectus produced circulatory delay in superior temporal or inferior temporal sectors, respectively, of the iris. When tenotomies of a horizontal and one or two vertical recti were combined, the defect occurred in the region of the vertical rectus only. Blood supply of the nasal half of the iris was usually not disturbed by tenotomy of the vertical and/or medial rectus. The findings indicate that the blood supply of the iris is segmental and suggest that, in strabismus surgery, cutting the two vertical recti along with the lateral rectus may subject the eye to the risk of anterior segment ischemia. (13 figures, 2 tables, 28 references)—Authors' abstract

OCULAR INVOLVEMENT IN WHIPPLE'S DISEASE. Font, R. L., Rao, N. A., Issarescu, S., and McEntee, W. J. (Ophthalmic Path., Armed Forces Inst. Path., Washington, D.C.). Arch. Ophthalmol. 96:1431, 1978.

A 52-year-old man had a prolonged history of nondeforming migratory polyarthritis and a short episode of pericarditis preceding the onset of bilateral vitreitis and retinitis. The clinical course was characterized by progressive deterioration of vision, increasing lethargy, and dementia, leading to coma and death from pneumonia (21 months later). No intestinal manifestations were recorded. Both eyes, which were removed postmortem, disclosed numerous PAS-positive macrophages throughout the inner retina and vitreous. Electron microscopic studies of the macrophages displayed intracytoplasmic, degenerating, rod-shaped bacteria and membranous structures identical to those seen in the intestine, brain, heart, and other tissues of patients with Whipple's disease. Clinicians should include Whipple's disease, and reticulum cell sarcoma, in the differential diagnosis of patients with bilateral retinitis and vitreitis, especially if these disorders are associated with CNS manifestations. (7 figures, 24 references)—Authors' abstract

British Journal of Ophthalmology

MEASLES RETINOPATHY DURING IMMUNOSUPPRESSION. Haltia, M., Tarkkanen, A., Vaheri, A., Kaakinen, K., Paetau, A., and Erkillä, H. (Depts. Pathol., Ophthalmol. and Virol., Univ. Helsinki, Helsinki, Finland). Br. J. Ophthalmol. 62:356, 1978.

After surgery for a rhabdomyosarcoma of the testis without clinical signs of metastases, the 13-year-old patient was placed on cytotoxic chemotherapy on which he did well for one year; at the end of the year he contracted measles and died after three months of illness. Ophthalmoscopically, the patient showed, two weeks before his death, irregular, flat areas of depigmentation and one greyish elevated lesion below one macula. The autopsy revealed no extra- or intracranial metastases of the original malignancy, but, histologically, there were clear-cut signs of measles encephalopathy. By light microscopy numerous intranuclear inclusion bodies were found in oligodendroglial cells and in neurons of the brain, particularly in the region of the lentiform nuclei and in the internal capsule. The inclusion bodies consisted of masses of tubular structures with the ultrastructural and immunofluorescent properties of measles virus nucleocapsids. The prominent histological eye finding was patchy, focal, retinal necrosis surrounded by large areas of almost normal retina. As in the brain, there was total absence of inflammatory cells and of any attempt at repair, except for a few macrophages. The choroid was entirely normal. By electron microscopy, some of the remaining nuclei of the inner nuclear layer (in the necrotic areas) appeared to contain structures resembling the nucleocapsids of paramyxoviruses; the same regions stood out by bright fluorescence on indirect immunofluorescence with hyperimmune antimeasles virus rabbit serum. The present case is analogous to several reported cases of unusually severe measles encephalopathy in children made immunodeficient by chemotherapy for leukemia. The new feature is the involvement of the retina which was recognized ophthalmoscopically and could be helpful in clinical differential diagnosis. (5 figures, 1 table, 26 references)—Peter C. Kronfeld

DOES ENUCLEATION OF THE EYE CONTAINING A MALIGNANT MELANOMA PREVENT OR ACCELERATE THE DISSEMINATION OF TUMOR CELLS? Zimmerman, L. E., McLean, I. W., and Foster, W. D. (Armed Forces Inst. of Pathol., Washington, D.C.). Br. J. Ophthalmol. 62:420, 1978.

The material which forms the backbone of

this paper is a series of 2652 patients with malignant melanoma of the choroid or ciliary body on whom, after enucleation of the tumor-containing eye and histopathological examination adequate follow-up information could be obtained. In the present communication the point is made that the value of enucleation as a life-prolonging form of therapy should, logically, be judged in the light of observations on the natural course of untreated melanomas. Pertinent statistical data are still not available, but it is widely believed and taught that uveal melanomas, unlike cutaneous melanomas, are rarely found to have metastasized when the patient is referred for treatment of the primary tumor. This belief is supported by the experience of the few observers who have had the opportunity to make accurate observations on untreated pigmented tumors of the uvea. If the annual death rate from untreated uveal malignant melanomas is assumed to be around 1%, then the data of the Armed Forces series are clearly indicative of a peak in annual death rate from metastases, amounting to about 8%, in the middle of the second year after the enucleation. This peak is followed by a smooth decline to the 1% annual death rate which prevails during the second postoperative decade. This suggests that the surgical removal of the tumor-containing eye by conventional techniques promotes dissemination of tumor cells. Guided by this concept, Fraunfelder et al. have recommended "no touch" techniques for the diagnostic management and the enucleation of eyes harboring a melanoma suspected, on clinical grounds, of being malignant. These recommendations are strongly endorsed by the present authors. (3 figures, 28 references)—Peter C. Kronfeld

Developmental Medicine and Child Neurology

CORTICAL BLINDNESS ASSOCIATED WITH OCCIPITAL ATROPHY: A COMPLICATION OF *H. influenzae* MENINGITIS. Margolis, L. H., Shaywitz, B. A., and Rothman, S. G. (Yale Univ. School of Med., New Haven, Conn.). Dev. Med. Child Neurol. 20:490, 1978.

A three-year-old child with *H. influenzae* meningitis developed cortical blindness. Computerized tomography demonstrated occipital hemorrhage, and a subsequent scan showed occipital atrophy. This is the first description of cortical blindness secondary to meningitis with an associated anatomical defect. (2 figures, 9 references)—Authors' abstract

Experimental Eye Research

A FLUOROPHOTOMETRIC STUDY OF THE EFFECT OF TOPICAL TIMOLOL ON AQUEOUS HUMOR DYNAMICS. Yablonski, M. E., Zimmerman, T. J., Waltman, S. R., and Becker, B. (Dept. Ophthalmol., Washington Univ. School of Med., St. Louis, Mo.). Exp. Eye Res. 27:135, 1978.

A modification of the fluorophotometric method of Jones and Maurice is described and used to measure the aqueous flow coefficient. The method was used to measure the effect of topical timolol on aqueous humor dynamics in 15 human subjects. It was found that the acute decrease in intraocular pressure caused by timolol can be explained entirely by its effect on the aqueous flow. The mean aqueous flow coefficient in the timolol treated eye was found to be 0.0126 min^{-1} before timolol, and 0.0067 min^{-1} after timolol. A small effect on the aqueous flow coefficient of the untreated eye was also observed. (1 figure, 3 tables, 13 references)—Authors' abstract

THE FATE OF ANTERIOR CHAMBER FLUORESCEIN IN THE MONKEY EYE. Sherman, S. H., Green, K., and Laties, A. M. (Dept. of Ophthalmol., Scheie Eye Inst., Univ. Pennsylvania Med. School, Philadelphia, Pa.). Exp. Eye Res. 27: 159, 1978.

As defined by freeze-dry tissue techniques, there are two distinct routes by which fluorescein leaves the anterior chamber of the living rhesus monkey eye: (1) the conventional pathway—within five minutes of the initiation of fluorescein perfusion through the anterior chamber, the conventional pathway filled, tracer passes through the trabecular meshwork into Schlemm's canal, and flowed back within scleral and episcleral venous derivatives to enter large veins in the extraocular muscles; (2) the uveo-vortex pathway—fluorescein rapidly moved into the iris stroma and into the anterior part of the ciliary body. The anterior chamber border of the ciliary body is little

more than a sparse mesh from which fluorescein entered directly into the substance of the anterior ciliary muscle. Fluorescein penetrated blood vessels in the iris stroma and in the anterior ciliary body from where it could be traced posteriorly to the equatorial choroid and vortex veins. The specific sequential tissue distribution of fluorescein strongly supports the existence of a uveo-vortex pathway for aqueous outflow. (12 figures, 28 references)—Authors' abstract

Journal of Clinical Endocrinology and Metabolism

RESPONSES TO TRH AND T^3 SUPPRESSION TESTS IN EUTHYROID SUBJECTS WITH A FAMILY HISTORY OF GRAVES' DISEASE. Tamai, H., Suematsu, H., Ikemi, Y., Kuma, K., Matsuzuka, R., Kumagai, L. F., Shizume, K., and Nagataki, S. (Dept. Psychosomatic Med., Faculty of Med., Kyushu Univ., Fukuoka, Japan). J. Clin. Endocrinol. 47:475, 1978..

The authors studied TRH responsiveness, T^3 suppressibility and thyroidal antibodies in clinically and chemically euthyroid relatives of patients with Graves' disease. Abnormal levels in each area of testing were noted in significant, although not coincident, percentages of those tested. The authors speculate that abnormal responses in these tests by relatives of patients with Graves' disease might foreshadow overt hyperthyroidism and they recommend follow-up studies. (3 figures, 3 tables, 17 references)—Gerald Harris

Laboratory Investigation

EXPERIMENTAL INJURY OF THE OPTIC NERVE WITH OPTIC DISK SWELLING. Baumbach, G. L., Cancilla, P. A., Hayreh, M. S., and Hayreh, S. S. (Depts. Path. and Ophthalmol., College of Med., Univ. of Iowa, Iowa City, Ia.). Lab. Invest. 39:50, 1978.

An ultrastructural study utilizing horseradish peroxidase was performed to determine the mechanism and consequences of leakage of vascular protein following injury of the optic nerve. Unilateral optic nerve injuries were produced in four rhesus monkeys by making a cautery lesion on the retrobulbar portion of the optic nerve. Optic disk changes were followed with stereo fundus photography and fluorescein angiography. Three to 14 days after injury horseradish peroxidase was given intravenously and the tissue was prepared for electron microscopy, including serial sections of selected tissue blocks. Fundus photography and fluorescein angiography showed edema of the optic disk in two animals. There was leakage of horseradish peroxidase into the optic nerve head from the optic nerve lesion and the peripapillary choriocapillaris. Although the pathway of horseradish peroxidase leakage in the injured optic nerve was not entirely clear, serial sections indicated intraendothelial channels as one possible route. Alterations of the optic nerve head were confined to the axon segments anterior to the injury, and included aggregation of mitochondria, disruption of neurotubules, and swelling. These findings suggest that optic nerve injury produces damming of axoplasmic flow and that swelling of the optic nerve head is the result of axon enlargement. (9 figures, 1 table, 66 references)—Authors' abstract

Medicine

MYASTHENIA GRAVIS IN PATIENTS WITH THYMOMA, WITH PARTICULAR REFERENCE TO ONSET AFTER THYMECTOMY. Namba, T., Brunner, N. G., and Grob, D. (Dept. Med., Maimonides Med. Ctr., State Univ. of New York, Brooklyn, N.Y.). Medicine 57:411, 1978.

Approximately one third of patients with thymoma have myasthenia gravis and one tenth of patients with myasthenia gravis have a thymoma. In two thirds of myasthenic patients the thymus is hyperplastic and contains germinal centers. It has long been suspected that the thymus may play a role in the pathogenesis of myasthenia gravis. Since the thymus is required for functional maturation of T lymphocytes that mediate cellular immune responses, and contains in germinal centers B lymphocytes that secrete immunoglobulins mediating humoral immune responses, the thymic abnormalities in myasthenic patients are presumed to be related to the immunologic alterations that occur in this disease. However, it is not yet known if the thymic abnormalities are related to, or necessary for, the development of the neuromuscular block that characterizes the disease. The current study analyzes

the incidence of myasthenia gravis in 72 patients with thymoma studied by the authors, and in 1,655 patients previously reported by others. Of particular interest are seven patients who were observed to develop myasthenia gravis after total thymectomy for removal of a thymoma, and 26 patients previously reported by others. The onset of myasthenia gravis in these patients in the absence of the thymus suggests that the role of the thymus in the pathogenesis of myasthenia gravis may be indirect and initiated prior to thymectomy. (4 figures, 4 tables, 150 references)—Authors' abstract

Neurology

UVEITIS, PERIVENOUS SHEATHING AND MULTIPLE SCLEROSIS. Bamford, C. R., Ganley, J. P., Sibley, W. A., and Laguna, J. F. (Dept. of Neurol., Univ. Arizona Health Sci. Ctr., Tucson, Ariz.). Neurology 28:119, 1978.

Pars planitis (peripheral uveitis) and perivenous sheathing are two ocular phenomena associated with multiple sclerosis. The incidence of pars planitis in 127 multiple sclerosis patients was 2.4%. This is lower than that reported by others but significantly higher than its occurrence in the general population. The incidence of perivenous sheathing (11%) is consistent with the experience of others. However, this find was noted more frequently in patients with a progressive form of multiple sclerosis. No perivenous sheathing was found to develop within the first few weeks following 31 exacerbations, and no association was identified between its presence and the severity of neurologic disability. (5 figures, 6 tables, 16 references)—Authors' abstract

New England Journal of Medicine

OPTIC NEUROPATHIES. Lessell, S. (Boston Univ. School of Med., Boston, Mass.). N. Engl. J. Med. 299:533, 1978.

Three specific neuropathies are reviewed here: ischemic optic neuropathy, optic neuritis, and infiltrative-compressive optic nerve disease. Each section in a few paragraphs capsulizes the important diagnostic and therapeutic points for each entity. For example, to make the diagnosis of ischemic optic neuropathy, there should be either an elevated erythrocyte sedimentation rate or a positive temporal artery biopsy or both. If neither is present, in spite of the eye findings, the patient should probably not be subjected to the risks of prolonged high dosage corticosteroid therapy. Generally, optic neuritis falls into two groups—those with other lesions in the white matter of the central nervous system (presumably multiple sclerosis) and those who have no other neurologic disorder. The risk of developing multiple sclerosis in the latter group is somewhere between 30 and 50%. The final word on the treatment of optic gliomas has not been written but the author leans toward the nonoperative management when the tumor is primarily in the nerve and has not invaded the cranial cavity. (1 figure)—David Shoch

Ophthalmology

IS BLINDNESS A REALISTIC COMPLICATION IN BLEPHAROPLASTY PROCEDURES? Waller, R. R. (Dept. Ophthalmol., Mayo Clinic, Rochester, Minn.). Ophthalmol. 85:730, 1978.

Blindness is a rare but realistic complication in blepharoplasty procedures. Review of 55 case reports in the literature supports this view. The cause or causes of blindness are not precisely clear, but orbital hemorrhage after removal of fat seems to be the most common event associated with visual loss. Preoperative ophthalmologic assessment is highly desirable to document preexistent eye and systemic disease. Exquisite care with removal of fat is essential. Careful postoperative observation without patching is necessary. Management of acute visual loss may be medical, surgical, or both. (24 references)—Authors' abstract

Plastic and Reconstructive Surgery

EARLY SKELETAL RELEASE IN THE INFANT WITH CRANIOFACIAL DYSOSTOSIS. McCarthy, J. G., Coccaro, P. J., Epstein, F., and Converse, J. M. (Inst. of Reconstr. Plast. Surg., New York Univ. Med. Ctr., New York, N.Y.). Plast. & Reconstr. Surg. 62:335, 1978.

Craniofacial dysostosis involves premature fusion of cranial sutures, resulting in cranial and facial deformity. Depending on the su-

tures affected, the orbits may be shallow with resultant proptosis. Established surgical techniques include strip craniectomies in infancy to remove the synostosed suture (usually coronal) to allow greater expansion of the calvarium. The authors emphasize that the sphenozygomatic suture is anatomically continuous with the corneal suture and that synostosis of this and other small sutures at the cranial base are overlooked in classical procedures, allowing persistence of orbital deformity. They propose extension of the strip craniectomy to include the sphenozygomatic suture. Early results in ten cases are encouraging. The authors hope that such an approach in selected cases would eliminate a need for the later, more extensive, craniofacial reconstructions recently popularized. (10 figures, 14 references)—Gerald Harris

Science

PHYSIOLOGICAL BASIS OF ANISOMETROPIC AMBLYOPIA. Eggers, H. M., and Blakemore, C. (Physiological Lab., Cambridge, England). Science 201:264, 1978.

Anisometropic amblyopia is a developmental disorder of vision: babies with uncorrected differences in refractive power in the two eyes are often left later in life with defective vision in one eye, which cannot then be rectified optically and which is not caused by any obvious retinal or ocular pathology. It is known that even a brief occlusion of one eye will cause changes in the visual cortex of kittens. The authors investigated the possibility that a similar mechanism is at work in anisometropia. They therefore reared five kittens in a totally dark room except for an hour or two each day when each animal wore a pair of goggles containing a high minus sphere in front of one eye. When the visual cortex was examined it was found that most neurons were dominated by input from the normal eye. Moreover, contrast sensitivity and resolving power were lower for stimulation through the originally defocused eye mimicking psychophysieal results from human anisometropic amblyopes. (3 figures, 26 references)—David Shoch

Transactions of the American Ophthalmological Society

ORBITAL VENOGRAPHY: ANATOMY, TECHNIQUE, AND DIAGNOSTIC USE. (Thesis) Dayton, G. O. (Dept. Ophthalmol. and Radiological Sciences, Univ. California Ctr. for Health Sciences, Los Angeles, Calif.). Tr. Am. Ophthalmol. Soc. 75:459, 1977.

Orbital venography has lost a great deal of its attraction to ophthalmologists since the introduction of computerized tomography. However it still has some value particularly for lesions in the area of the orbital apex and cavernous sinus where computerized tomography is poorest. The cavernous and basal venous sinuses of the brain can be outlined for various filling defects by orbital venography providing a diagnosis without resorting to more dangerous and involved procedures that are less specific. (17 figures, 5 tables, 53 references)—David Shoch

CHROMOSOMAL ABNORMALITIES ASSOCIATED WITH CYCLOPIA AND SYNOPHTHALMIA. (Thesis) Howard, R. O. (Yale Univ. School of Med., New Haven, Conn.). Tr. Am. Ophthalmol. Soc. 75: 505, 1977.

Cyclopia is a fairly rare anomaly and of the 31 case reports of human cyclopia, 24 showed definite abnormalities of chromosomes. The most common abnormality is trisomy for D group chromosome. Seventeen of the 24 had this abnormality. According to the present understanding of chromosomal disorders, an individual with a trisomic anomaly would code for the production of excessive enzymes, proteins, controlled genes and organizers corresponding to the genes present in the extra chromosome. (8 figures, 3 tables, 86 references)—David Shoch

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.

700 North Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least three months before the date of occurrence.

INTERNATIONAL SOCIETY FOR CLINICAL ELECTROPHYSIOLOGY OF VISION

The International Society for Clinical Electrophysiology of Vision will hold its 17th Symposium in "Schloss Reinhardsbrunn," Friedrichronda, German Democratic Republic, June 5-10, 1979. Topics to be discussed are "Visual electrodiagnosis in systemic diseases," and "Visual electrophysiology and localized retinal stimulation." The official language of the Symposium is English. For further information and registration, write Professor Dr. E. Schmoger, Augenklinik der Medizinische Akademie, Nordhauserstrasse 74, 50 Erfurt German Democratic Republic.

INTERNATIONAL SYMPOSIUM: NEUROCHEMISTRY OF THE RETINA

An international symposium on neurochemistry of the retina will be held in Athens, Greece, Aug. 28-Sept. 1, 1979. Topics to be discussed include the following: composition, metabolism, and biogenesis of membranes; biochemical approaches to the study of visual cells and their relationship to the pigment epithelium; chemical transmission of nerve signals; biochemical studies on retinal receptors, photoreceptors, and phototransduction; cyclic nucleotides; biochemical and pharmacological approaches to study the entire retina; neurochemical studies in experimental diabetic retinopathy, retinal degenerative diseases, sphingolipidoses, amino acid disturbances; and future research from neurchemical studies of the retina in health and diseases. For further information, write Nicholás G. Bazán, Chairman, Organizing and Scientific Committees, Instituto de Investigaciones Bioquímicas, Universidad Nacional del Sur CONICET, Av. Alem 1253, 8000-Bahía Blanca, Argentina.

UNIVERSITY OF CHICAGO: ANNUAL ALUMNI DAY

The Department of Ophthalmology of the University of Chicago holds its Annual Alumni Day March 7, 1979. The guest speaker is Albert M. Potts, chairman, Department of Ophthalmology, University of Louisville. The staff and residents of departments of ophthalmology, alumni, and other physicians are invited. The full-day session will include a scientific program, a buffet luncheon, and reception. Registration and scientific session are scheduled to begin at 9 AM in P-117, Albert Merritt Billings Hospital, Chicago, Illinois. There is no charge. For further information, write Mrs. Karin Cassel, Department of Ophthalmology, 950 E. 59th St., Chicago, IL 60637; telephone (312) 947-6063.

TORONTO: CONTACT LENS CONFERENCE

A comprehensive contact lens meeting, including lecture programs and workshops, will be held April 20 and 21, 1979, at the Four Seasons Yorkville, Toronto, Canada. The meeting will cover all aspects of contact lens technology. Jack Hartstein will deliver the Second Maxwell K. Bochner Lecture. For further information, write Harold Stein, M.D., c/o the Park Plaza Hotel, 170 Bloor Street West, Toronto, Ontario, Canada M5S 1T9.

COMPUTERS IN OPHTHALMOLOGY: COURSE

A course in application of computers to ophthalmic patient care and clinical research will be held April 5 and 6, 1979, in St. Louis, Missouri. For further information, write Robert Greenfield, D. Sc., Biomedical Computer Laboratory, Washington University School of Medicine, 700 S. Euclid Ave., St. Louis, MO 63110.

UNIVERSITY OF PENNSYLVANIA ALUMNI OPHTHALMOLOGICAL ASSOCIATION: ANNUAL MEETING

The University of Pennsylvania Alumni Ophthalmological Association will hold its annual meeting on May 10-12, 1979. The subject of this year's symposium is "Practical Neuro-ophthalmology for the clinician." Melvin G. Alper, M.D., will give the second Annual Francis Heed Adler lecture. The registration fee is $200 for practicing ophthalmologists and $175 for University of Pennsylvania Ophthalmological alumni. The registration fee includes two luncheons and a cocktail party. Registration for residents with a letter from their program director is $75. Registration fee and request for additional information should be mailed to David M. Kozart, M.D., Program Coordinator, Scheie Eye Institute, 51 N. 39th St., Philadelphia, PA 19104.

GEORGETOWN UNIVERSITY CENTER FOR SIGHT: CLINICAL OPHTHALMOLOGY CONFERENCE

The Office of Continuing Medical Education and the Department of Ophthalmology of Georgetown University School of Medicine will offer a clinical ophthalmology conference, "Diagnosis and management of the office patient," in Hamilton, Bermuda, Feb. 5-8, 1979. For further information, write Office of Continuing Medical Education, Georgetown University School of Medicine, Room 412 KoberCogan, 3800 Reservoir Rd., N.W., Washington, DC 20007; telephone (202) 625-2306.

SOUTHERN CALIFORNIA PERMANENTE MEDICAL GROUP: SECOND ANNUAL OPHTHALMOLOGY SYMPOSIUM

The Southern California Permanente Medical Group and the University of California, San Diego, will hold the Second Annual Ophthalmology Symposium, "Diagnosis and management of corneal external disease and contact lens problems," July 13 and 14, 1979, at the Hilton Hotel, San Diego, California. For further information, write Southern California Permanente Medical Group, Education Office, 4647 Zion Ave., San Diego, CA 92120; telephone (714) 563-2558.

DOCTOR-TO-DOCTOR MEDICAL JOURNAL PROGRAM

Doctors in the United States are asked to send their medical journals—after having read them—to colleagues overseas (Asia, Latin America, and Africa) who wish to have access to current medical literature but because of either currency regulations or actual costs involved, cannot themselves subscribe to medical periodicals. Participants will be supplied with the name, address, and medical specialty of doctors, in these areas who wish to receive much-wanted journals (particularly specialty journals) and will mail them directly to their overseas colleague. The "Doctor-to-Doctor" program is sponsored by the American Medical Association with the collaboration of the World Medical Association. Persons wishing to participate in the program should send their names, addresses, and title of journals they would be willing to contribute to Doctor-to-Doctor Program, c/o The World Medical Association, Inc., 10 Columbus Circle, New York, NY 10019.

PERSONALS

H. DWIGHT CAVANAGH

H. Dwight Cavanagh has been appointed F. Phinizy Calhoun Professor and Chairman of the Department of Ophthalmology, Emory University School of Medicine, Atlanta, Georgia.

GISSUR J. PETURSSON

Gissur J. Petursson has been named acting chairman and assistant professor of the Department of Ophthalmology at the University of Arkansas, Little Rock.

HAROLD G. SCHEIE

Harold G. Scheie founding director of Scheie Eye Institute, received the Ephraim D. Saunders Award of the Presbyterian-University of Pennsylvania Medical Center in Philadelphia Sept. 21, 1978. The award, named in honor of Presbyterian's founder, is the highest honor that can be bestowed on an individual by the medical center. Dr. Scheie was also named an honorary trustee at the ceremonies.

New Research Grants Awarded by the National Eye Institute

July 1, 1978 to September 30, 1978

RESEARCH PROJECT GRANTS

Institution	Principal Investigator	Title of Project	Costs Awarded
Medical College of Georgia Augusta, Georgia	Ata A. Abdel-Latif	Metabolism and function of glycerolipids in the iris	$ 46,636
City College of New York New York, New York	Robert R. Alfano	The fast kinetics of the primary visual processes	110,179
Princeton University Princeton, New Jersey	Meredithe L. Applebury	Biochemistry of photoreceptor cells	52,581
Albany Medical College Albany, New York	David W. Appleby	DNA size and genome organization in lens cells	77,689
University of Texas Galveston, Texas	John C. Barber	Tissue stabilized alloplastic corneal prosthesis	65,267
University of Illinois Chicago, Illinois	Louis A. Benevento	Visual, sensory, motor and associational systems	55,600
University of Washington Seattle, Washington	Richard E. Bensinger	Superoxide dismutase: transport, aging and degeneration	54,457
Adelphi University Garden City, New York	Frederick A. Bettelheim	Light scattering parameters of cataractous lenses	21,985

Institution	Principal Investigator	Title of Project	Costs Awarded
University of Minnesota Saint Paul, Minnesota	Stephen I. Bistner	Hereditary cataract: anatomic-metabolic changes	$ 57,574
University of California Irvine, California	Robert H. Blanks	Eye movement control	88,064
University of Washington Seattle, Washington	Ronald G. Boothe	Development of spatial vision	69,115
Mayo Foundation Rochester, Minnesota	William M. Bourne	Studies of the cornea	76,377
University of Tennessee Knoxville, Tennessee	Ned Buyukmihci	Effects of scrapie on hamster retina and optic nerve	36,015
Kirksville College of Osteopathic Medicine Kirksville, Missouri	Richard J. Cenedella	A new animal model for cataracts: study of mechanism	26,808
University of Michigan Ann Arbor, Michigan	Bruce E. Cohan	The optic disc: quantitation of topography	119,920
Mount Holyoke College South Hadley, Massachusetts	Joseph D. Cohen	Adaptation in normal and deficient color vision	43,955
Marine Biological Laboratory Woods Hole, Massachusetts	Donald E. Copeland	Secretion of aqueous, vitreous humor in fish eye	36,207
University of Rochester Rochester, New York	Thomas R. Corwin	Psychophysical diagnosis of retinitis pigmentosa	50,571
University of Rochester Rochester, New York	Manuel Del Cerro	Pathogenesis of retinal immunopathologies	54,818
University of Washington Seattle, Washington	Margaret V. Dobson	Clinical assessment of visual acuity	70,782
Columbia University New York, New York	Howard M. Eggers	Animal model of amblyopia	11,590
State University of New York Stony Brook, New York	Gustav A. Engbretson	Visual information processing by the parietal eye	65,700
University of California Los Angeles, California	Debora A. Farber	Cyclic nucleotides in cone metabolism and disease	81,736
Wayne State University Detroit, Michigan	Robert N. Frank	A proposed model for diabetic retinopathy	38,473
Columbia University New York, New York	Peter Gouras	Neurophysiology of primate vision	196,099
Rockefeller University New York, New York	John D. Gregory	Biosynthesis and turnover of proteoglycans in cornea	48,720
University of Pittsburgh Pittsburgh, Pennsylvania	Richard W. Hall, Jr.	Implementations of visual information processing	13,647
Southern Illinois University Carbondale, Illinois	Paul A. Hargrave	Rhodopsin topography in the rod cell disk membrane	83,512

Institution	Principal Investigator	Title of Project	Costs Awarded
Massachusetts Institute of Technology Cambridge, Massachusetts	Richard M. Held	Development of amblyopia in early cataract and strabismus	$ 47,968
University of Miami Miami, Florida	Jonathan Herschler	Aqueous humor and conjunctival fibroblasts	57,819
Johns Hopkins University Baltimore, Maryland	Lawrence W. Hirst	Assessment of corneal endothelium in vivo	68,887
Washington University Saint Louis, Missouri	Charles P. Hughes	Visual function in ventral lateral geniculate	37,586
Columbia University New York, New York	Frederick A. Jakobiec	Ocular lymphoid tumors: immunology and ultrastructure	108,753
University of Illinois Chicago, Illinois	Lee M. Jampol	A longitudinal study of hypertensive retinopathy	50,818
Baylor College of Medicine Houston, Texas	Dan B. Jones	Endogenous fungal endophthalmitis	108,327
Ohio State University Columbus, Ohio	Ronald Jones	Clinical implications of vergenceanomaly	44,540
Upstate Medical Center Syracuse, New York	Gregory E. Keating	Recovery from cortical blindness	64,811
John Carroll University University Heights, Ohio	Max J. Keck	Intraocular transfer of after-effects in strabismus	26,502
University of Alabama Birmingham, Alabama	Robert N. Kleinstein	Visual field defects with blood pressure therapy	48,150
Baylor College of Medicine Houston, Texas	Frank L. Kretzer	Retina: ultrastructure of photoreceptors	26,151
New York University New York, New York	David L. Krohn	Corneal penetration of pilocarpine via liposomes	34,099
Yale University New Haven, Connecticut	Yin-Lok Lai	Peripheral retinal degeneration in Fischer rats	63,685
Baylor College of Medicine Houston, Texas	Dominic M. Lam	Development and regeneration of the vertebrate retina	84,276
Georgetown University Washington, DC	Michael A. Lemp	Effect of systemic drugs on tear production	44,158
Eye Research Institute of Retina Foundation Boston, Massachusetts	Hsiao-su Liu	Sustained-released chemotherapy for ocular malignancy	89,803
Mayo Foundation Rochester, Minnesota	James C. Lynch	Oculomotor control mechanisms of the cerebral cortex	68,768
Marine Biological Laboratory Woods Hole, Massachusetts	Edward F. Mac Nichol, Jr.	Studies of single visual receptor cells	113,686
Stanford University Stanford, California	Lawrence H. Mathers	Trophism in the developing nervous system	50,889

Institution	Principal Investigator	Title of Project	Costs Awarded
University of California Santa Cruz, California	Melanie J. Mayer	Development of antisotropic visual sensitivity	$ 40,639
University of Pennsylvania Philadelphia, Pennsylvania	David S. McDevitt	Crystallins in normal and regenerated newt eye lenses	49,297
University of Tennessee Center for Health Sciences Memphis, Tennessee	Barbard J. McLaughlin	Photoreceptor synatogenesis in the retina	47,588
University of California Los Angeles, California	Roberta L. Meyers	HLA and immune factors in ocular herpes	33,782
University of Kansas Lawrence, Kansas	Thomas J. Mikkelson	Quantitation of drug uptake by corneal epithelium	34,133
Santa Clara Valley Medical Center San Jose, California	Laughton E. Miles	Chronobiological disorders in blind people	82,401
Johns Hopkins University Baltimore, Maryland	Neil R. Miller	Clinical investigations in ocular motility disorders	71,213
Mount Sinai School of Medicine New York, New York	Thomas W. Mittag	Drug effects on iris and ciliary body adenylate cyclase	84,844
Worcester Polytechnic Institute Worcester, Massachusetts	Audrey L. Muggleton-Harris	Cataract and lens deterioration due to maturation	95,344
Wills Eye Hospital Philadelphia, Pennsylvania	Rose M. Nagy	Heterogeneity of lymphocytes in herpes ocular disease	62,588
Louisiana State University New Orleans, Louisiana	Randall J. Olson	Corneal physiology and keratoplasty induced glaucoma	48,550
University of California Los Angeles, California	Edward M. Ornitz	Maturation of vestibular nystagmus	81,548
University of Utah Salt Lake City, Utah	Jeffrey D. Owen	CA 2+ electrode measurements in limulus photoreceptors	74,400
University of Alabama Birmingham, Alabama	Clyde W. Oyster	Neural interaction in the vertebrate retina	48,375
Purdue University West Layfayette, Indiana	William L. Pak	Conductance fluctuations in photoreceptors of limulus	27,821
Duke University Durham, North Carolina	Richard A. Palmer	Photoacoustic spectroscopy of the aging lens	54,000
National Autonomous University of Mexico Mexico, Mexico	Herminia Pasantes-Morales	Taurine and ionic fluxes in retina	15,140
University of Kansas Lawrence, Kansas	Thomas F. Patton	Age-related dosage modifications for ophthalmic drugs	43,190
Johns Hopkins University Baltimore, Maryland	Arnall Patz	Diabetic retinopathy: inhibition of neovascularization	113,150

Institution	Principal Investigator	Title of Project	Costs Awarded
Purdue University West Lafayette, Indiana	Lawrence H. Pinto	Mammalian visual mutants	$ 59,071
Eye Research Institute of Retina Foundation Boston, Massachusetts	Oleg Pomerantzeff	The krypton laser in photocoagulation therapy	134,069
Eye Research Institute of Retina Foundation Boston, Massachusetts	Oleg Pomerantzeff	High resolution, wide-angle TV ophthalmoscope	127,410
University of Alabama Birmingham, Alabama	Josef T. Prchal	Cataract therapy RBC abnormalities in diabetics	78,853
University of Pennsylvania Philadelphia, Pennsylvania	Edward N. Pugh, Jr.	Analysis of the mechanisms of photoreceptor kinetics	54,746
Yale University New Haven, Connecticut	Pasko T. Rakic	Prenatal development of the primate visual system	117,811
Joslin Diabetes Foundation Boston, Massachusetts	Lawrence I. Rand	Case control study of diabetic retinopathy	198,870
Rockefeller University New York, New York	Floyd Ratliff	Visual stimulator/data analyzer for clinical research	82,036
Massachusetts Eye and Ear Infirmary Boston, Massachusetts	Thomas M. Richardson	Tissue elements in the trabecular meshwork	66,149
University of Pennsylvania Philadelphia, Pennsylvania	Alan C. Rosenquist	Extrageniculate visual pathways in animals	85,442
New York University New York, New York	Kalman Rubinson	Retinal development and transformation of the lamprey	48,204
Wills Eye Hospital Philadelphia, Pennsylvania	Peter J. Savino	Host immunologic response in Graves' ophthalmopathy	34,833
Bishop College Dallas, Texas	Ronald A. Schachar	Ramans spectroscopy of the lens of the eye	45,539
University of California Los Angeles, California	Madelenine L. Schlag-Rey	Single unit studies of visuo-oculomotor mechanisms	63,680
University of Rochester Rochester, New York	David A. Scott	Eye development: growth cone structure in drosophilia	25,871
Temple University Philadelphia, Pennsylvania	Joel B. Sheffield	Retinal histogenesis studies	60,040
Johns Hopkins University Baltimore, Maryland	Arthur M. Silverstein	The pathobiology of the cornea	99,603
University of Massachusetts Amherst, Massachusetts	Robert J. Smyth, Jr.	A genetic eye defect and amelanosis in the chicken	68,384
New York Medical College New York, New York	Louis A. Southren	Studies of glucocorticoid induced induced cataract	94,558
University of Wisconsin Madison, Wisconsin	Peter D. Spear	Binocular interactions in visual system development	91,318

Institution	Principal Investigator	Title of Project	Costs Awarded
University of Texas Medical Branch Galveston, Texas	Satish K. Srivastava	Studies of ocular manifestations in sphingolipidoses	$ 36,263
Yale University New Haven, Connecticut	Tsuneo Tomita	Cellular origin of transretinal potentials	104,757
University of Illinois Medical Center Chicago, Illinois	Mark O. Tso	Pathology of an inherited retinal dystrophy in animals	60,776
University of Wisconsin Madison, Wisconsin	Ulker Tulunay-Keesey	Motion of retinal image and contrast sensitivity	60,619
University of Rochester Rochester, New York	John R. Tuttle	Quantitive analysis of necturus retinal network	45,091
Eye Research Foundation Columbia, Missouri	Ronald J. Walkenbach	Control of corneal physiology by cyclic nucleotides	74,654
University of Iowa Iowa City, Iowa	Robert C. Watzke	Toxocara canis infection of the primate eye	41,572
University of Oregon Health Sciences Center Portland, Oregon	Richard G. Weleber	Gyrate atrophy of the choroid and retina	74,993
University of Virginia Charlottesville, Virginia	James R. Wilson	Development of central visual pathways	58,816
Cornell University Medical Center New York, New York	Jacqueline M. Winterkorn	Visual behavior following paralytic strabismus	71,795
University of Minnesota Minneapolis, Minnesota	Jonathan D. Wirtschafter	Anterior chamber fluid acetylcholine concentration	55,210
University of Oregon Health Sciences Center Portland, Oregon	William R. Woodward	Mammalian visual system: neurotransmitter, screening	90,585
Columbia University New York, New York	Basil V. Worgul	Radiation cataractogenesis	81,340
University of Wisconsin Madison, Wisconsin	Tom C. Yin	Central nervous system control of eye movements	85,842
University of Illinois Medical Center Chicago, Illinois	Morton F. Goldberg	Ophthalmic research center core grant	90,339

CORE CENTER GRANTS AND SPECIALIZED RESEARCH CENTER GRANTS

Massachusetts Eye and Ear Infirmary Boston, Massachusetts	W. Morton Grant	Glaucoma clinical research center	$259,257
Massachusetts Institute of Technology Cambridge, Massachusetts	Richard M. Held	Central visual processes	147,929

National Research Service Award Fellowships

Institution	Principal Investigator	Title of Project	Costs Awarded
University of Pennsylvania Philadelphia, Pennsylvania	John R. Andrews	Picosecond kenetics of rhodopsin bleaching	$ 13,000
University of Texas Health Science Center Houston, Texas	Lisa B. Arbisser	Biochemical correlates of retinal degeneration	13,000
University of Chicago Chicago, Illinois	Diana J. Card	Development of the retino-geniculate pathways	14,500
Baylor College of Medicine Houston, Texas	Harold A. Cohen	E.M. of minimally denatured rod outer segment	9,934
University of Michigan Ann Arbor, Michigan	Jimmy D. Conner	Properties of isolated photo-receptors	13,000
Baylor College of Medicine Houston, Texas	Steven J. Fliesler	Lipid asymmetry in vertebrate photoreceptor membranes	13,000
Baylor College of Medicine Houston, Texas	William C. Gordon	Cyclic shedding in duplex retina of turtle	13,400
University of California Los Angeles, California	Richard E. Greenblatt	A quantitative study of toad road membrane currents	15,800
University of Texas Health Science Center Houston, Texas	Ashley R. Heath	Effects of intense light on the retina of fish	13,400
University of California San Francisco, California	Robert N. Hogan	Viral-induced retinal dysplasia in neonates	14,500
U.S. National Institutes of Health Bethesda, Maryland	Andrew P. Mariani	Avian retina: receptor interactions in horizontal cells	10,000
Stanford University Stanford, California	Gary G. Matthews	Cellular neurophysiology of the vertebrate	15,200
Mayo Foundation Rochester, Minnesota	Jay W. McLaren	Parietal-brainstem interactions and eye movement	13,800
Medical College of Georgia Augusta, Georgia	Thomas R. Morgan	The effect of selected rugs on aqueous humor dynamics	16,200
Florida State University Tallahassee, Florida	George D. Mower	Orientation selectivity in the visual system	13,800
Massachusetts Institute of Technology Cambridge, Massachusetts	Carl R. Olson	Anatomical analysis of oculo-motor pathways in animals	13,000
Eye Research Institute of Retina Foundation Boston, Massachusetts	Joel B. Piperberg	Steroid receptor molecules in the embryonic chick retina	13,400
California Institute of Technology Pasadena, California	Kathleen L. Rockland	Properties of afferents to medial visual area	13,000

Institution	Principal Investigator	Title of Project	Costs Awarded
Harvard University Boston, Massachusetts	Bruce J. Schnapp	Synaptic transmission in the barnacle visual system	$ 13,800
Columbia University New York, New York	Josette C. Seibles	Photoisomerization of sterically modified retinals	13,800
University of Cambridge Cambridge, United Kingdom	King W. Yau	Physiology of the vertebrate retina	13,200
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Eye Research Institute of Boston, Massachusetts	Alice J. Adler	Biochemical aspects of retinal adhesion	$ 31,060
Northern Illinois University De Kalb, Illinois	Robert R. Blake	Spatial vision in normal and visually deprived animals	29,697
University of Oregon Health Sciences Center Portland, Oregon	Ilene K. Gipson	Cell motility and adhesion during corneal wound healing	25,164
Columbia University New York, New York	Jong J. Lim	Endothelial cell adhesion and dielectric properties	33,128
University of California San Francisco, California	Thomas J. Ostwald	Ion transport and NA-K atpase of pigment epithelium	29,595
University of Pennsylvania Philadelphia, Pennsylvania	Edward N. Pugh, Jr.	Mechanisms of visual adaptation	35,942
Mount Sinai School of Medicine New York, New York	Robert H. Ritch	(NA+ + K+) – atpase in aqueous humor dynamics	34,701
New York University New York, New York	Helene E. Schaeffer	Transcorneal pilocarpine flux enhancement via liposomes	31,028
Johns Hopkins University Baltimore, Maryland	Tung-Tien Sun	Studies of corneal epithelial differentiation	26,309
INSTITUTIONAL NATIONAL RESEARCH SERVICE AWARDS			
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Stanford University Stanford, California	A. Ralph Rosenthal	Training in research in the basic sciences	56,104

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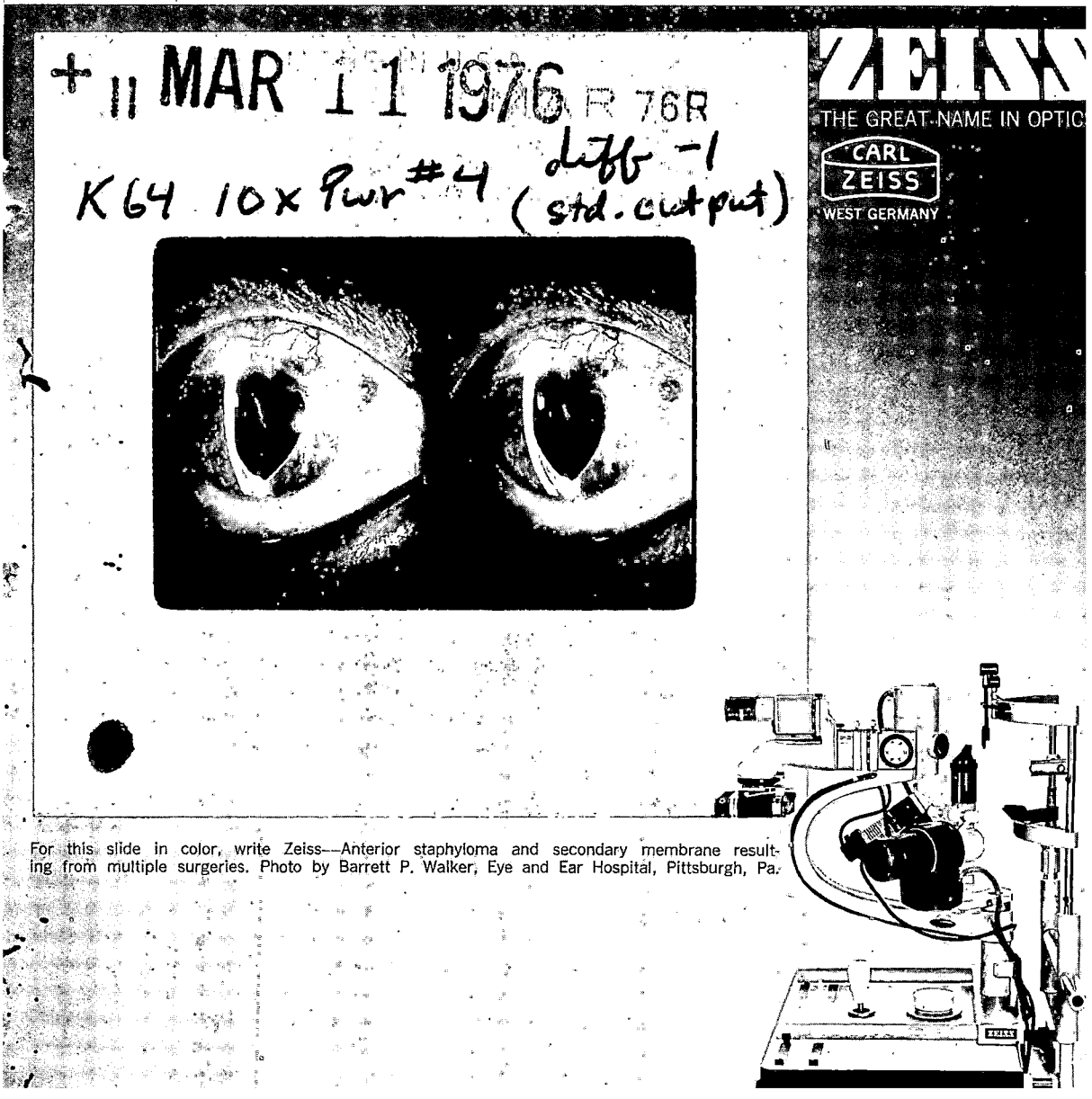
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LAWRENCE V. BASSO, M.D.—Palo Alto Medical Clinic, Palo Alto
STEVEN T. CHARLES, M.D.—Memphis, Tennessee
JOHN COLWELL, M.D.—University of So. Carolina, Charleston
JOSE CUNHA-VAZ, M.D.—University of Illinois Eye & Ear Infirmary, Chicago
HERBERT DAVIS, Ph. D.—University of Nebraska, Omaha
PETER H. FORSHAM, M.D.—University of California, San Francisco
ROBERT L. JACK, M.D.—Palo Alto Retinal Group & Stanford University, Menlo Park & Palo Alto
HOWARD B. LASSMAN, Ph. D.—Somerville, New Jersey
FRANCIS A. L'ESPERANCE, M.D.—Columbia-Presbyterian, New York City
HUNTER L. LITTLE, M.D.—Palo Alto Retinal Group & Stanford University, Menlo Park & Palo Alto
ARNALL PATZ, M.D.—Johns Hopkins, Baltimore
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1. Social Security Number or Taxpayer's Identification Number
2. Accountant or Estate Planner: Name, address, phone number
3. Attorney: Name, address, phone number
4. Employee(s): Name(s), address(es), phone number(s), details of termination of services
5. Insurance Agent (and/or Estate Planning Manager): Name, address, phone number
6. Stockbroker: Name, address, phone number
7. Trust (if established): Name of Trustee, address, phone number, name of bank's representative, phone, extension if the trustee is a bank
8. Will: Location, location of any codicils
9. Home: Location of deed, mortgage papers, etc.
10. Office: Location of deed or lease, mortgage papers, duration of lease or mortgage, provision for settling in event of death
11. Other real estate: Location(s) of deed(s) or mortgage paper(s)
12. Life Insurance: Location of policies
13. Other Insurance: Location of policies
14. Temporary coverage of the Practice: Name, address and phone number of an associate
15. Securities: Location of policies
16. Current unpaid bills: Location
17. Outstanding obligations: Notes, mortgages, pledges, charge accounts, credit checking accounts, etc. Details
18. Safety Deposit Box(es): Location(s), number(s), location of keys
19. Savings Account(s): Location(s) of passbook(s)
20. Checking Account(s): Location(s), location(s) of checkbook(s)
21. Financial Records: Location
22. Cash: Location of receipts, unbanked cash, source of cash for immediate needs
23. Tax Information: Location
24. Accounts Receivable: Location, the Doctor's views on collecting current and delinquent bills
25. Notes, loans, mortgages, etc., due from others: Location of items
26. Notifying patients: Method preferred by the doctor, location of appointment book
27. Notification: Hospital(s)—(Administrator), phone numbers: colleagues, phone numbers, Societies, etc., phone numbers
28. Veterans Administration: Branch of Service, date of discharge, service number, VA number(s), location of discharge papers
29. Blue Cross, etc.: Policy numbers of Blue Cross, Blue Shield and other Health Insurance (see later discussion)
30. Narcotics: Location of drugs, tax stamp, narcotics ledger, narcotics order book
31. Equipment (major): Purchase price, sales outlet
32. The Doctor's views on disposition of property, securities, anticipated income, etc.
33. Birth and Marriage Records: Location
34. Citizenship Papers (if applicable): Location

In addition to the foregoing but subject to the rights and duties of the Executor or Administrator, you may become involved with the following:

I. Probate of the Will: Your attorney will do this.

II. Disposition of narcotics, drug samples and medications. You should contact your Regional Office of the Bureau of Narcotics and Dangerous Drugs, U.S. Department of Justice, requesting disposition forms which must be completed and returned.

III. Patient Records:

A. These are important and confidential records which should be carefully preserved. Apparently there is no set limit of time specified by law.

B. The contents of such records should be disclosed to another physician only if the patient so requests. Such a request should be in writing and should be retained with the records. Normally, the records are confidential and diagnostic information in them should not be disclosed directly to the patient because of the risk that he might misinterpret them.

C. All patients' medical records should be kept for a minimum of ten years. Records of patients who were minors when treated should be preserved until two years after the patient reaches twenty-one. When possible, records should be kept for twenty-five years. It should be kept in mind that requirements for the retention of medical records may vary from state to state. Accordingly, before any medical records are destroyed or disposed of, local requirements should be verified with either the attorney for the estate or the local medical society. Financial records should be kept for five years, which is the statute of limitations on such information.

IV. Telephone: If there is an answering service, this can be a very helpful way of notifying patients of the Doctor's death with possible suggestions regarding their continued care. It is suggested that this service be retained for at least a month.

V. Notifying patients: Perhaps a simple sign on the office door "Call ———————— (office phone number)" will relieve you of the burden of contact with most of the patients and the answering service can take care of the matter.

If the physician's secretary is retained temporarily she might perform this service by being present during usual office hours. She also could notify patients with future appointments during this time.

VI. Taxes: The accountant and/or attorney should take care of all of this in connection with the financial records.

VII. Stopping advertising mail: It may take a year for knowledge of the Doctor's death to reach all the mailing lists; there is no central clearing office. You may perhaps choose to let it run out in this fashion, or you may write "Deceased return to sender" on each piece and mail it back. While the latter course might entail some effort initially, it will rapidly and effectively cut off the flow.

VIII. Insurance Agent and/or Trustee: A preliminary brief conference might be in order to settle the question of immediate funds, documents to be located, and arrangements for a later, detailed conference. Prompt notification of such people is important.

IX. Consideration of Sale of Practice: If the practice is to be sold, with or without real estate, relatively rapid action is advised, for it will quickly lose value. It can be advertised in the State Medical "Journal" and the "Journal" of the American Medical Association.

X. Real Estate: Except for practice-connected real estate, a hasty decision on sale or retention is not advised. It is hoped that the doctor has made known his views on this subject.

XI. Temporary coverage of patients:

A. Some arrangement with a colleague should be made immediately as regards patients in the hospital.

B. While not required, it would be a courtesy to be able to suggest a colleague to other patients.

XII. Insurance:

A. Malpractice Insurance: A refund on unused premiums may be possible. Find the policy and consult the local agent.

B. Liability and other Insurances: Certain policies issued with reference to the practice might have provisions for refund of unused premiums. Consult the issuing company or your insurance agent.

C. Health and Hospital Insurance: The survivor of a physician who had hospital or other health insurance under a group or family plan may keep such insurance, but it should be transferred to individual instead of family policies, unless you have dependent children.

XIII. Veterans Administration: If the Doctor was a Veteran, notify the Veterans Administration with the indicated information and apply for deserved benefits. Help with this can be had through the Veteran's Service Officer of the Doctor's county or district, or the Veterans Administration Regional Office. In this connection, save the Doctor's discharge papers permanently. It is possible that Pensions or other forms of remuneration may be provided in the future.

XIV. Social Security: Nearly all physicians are now covered by the Social Security Act. Visit the Social Security Office serving your area to find out what benefits are available to you. Be certain to have the Doctor's Social Security or Taxpayer Identification Number.

XV. Automobile(s): Title, if in Doctor's name, can be transferred with assistance of an automobile club, if a member, or through the Department of Motor Vehicles. Be sure insurance coverage is retained.

XVI. Equipment: It is best disposed of as part of the practice, if possible. Otherwise, it might be possible to obtain an estimate of value from one of the reputable equipment vendors and then sold either privately, through an advertisement in the State Medical "Journal" or to a dealer of used equipment. One of the Doctor's colleagues can give you the names of the major supply dealers serving your area.

XVII. Current bills: These must be paid, but not until the court has approved the Executor or appointed the Administrator of the Doctor's estate.

XVIII. Magazine subscriptions: Those purchased for office use might be checked for possible stoppage and subscription refund if you do not wish to continue them.

XIX. Dues: There is ordinarily no refund on Medical Society dues unless hardship exists.

XX. Securities: It is worth noting that Securities can be used as collateral for loans to meet financial needs. This may be preferable to selling the securities.

The American Society of Internal Medicine has learned with regret of the Doctor's death. We wish to extend our condolences. We realize that you will have many tasks in connection with settlement of the estate. To assist you the Society has prepared this pamphlet.

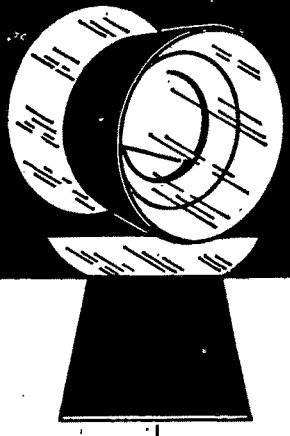
It should be pointed out that many of the items appearing herein are matters which, technically, will be the professional responsibility of the Executor (if the Doctor died with a Will) or the Administrator (if the Doctor died without a Will). However, the information contained herein may prove to be helpful not only to the person having this responsibility but also to the Doctor's survivor. We recommend that the survivor discuss the contents of this pamphlet with the Executor or Administrator of the Doctor's estate as soon as possible.

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OPHTHALMOLOGIST: 30, completing vitreous retinal fellowship with extensive surgical and medical experience. Will consider any potential opportunity in group or association. Box 152 AJO

WANTED: Ophthalmologist to join busy group in Fort Lauderdale, Florida. Must have training in retinal and vitreous surgery. Call 305-484-0700.

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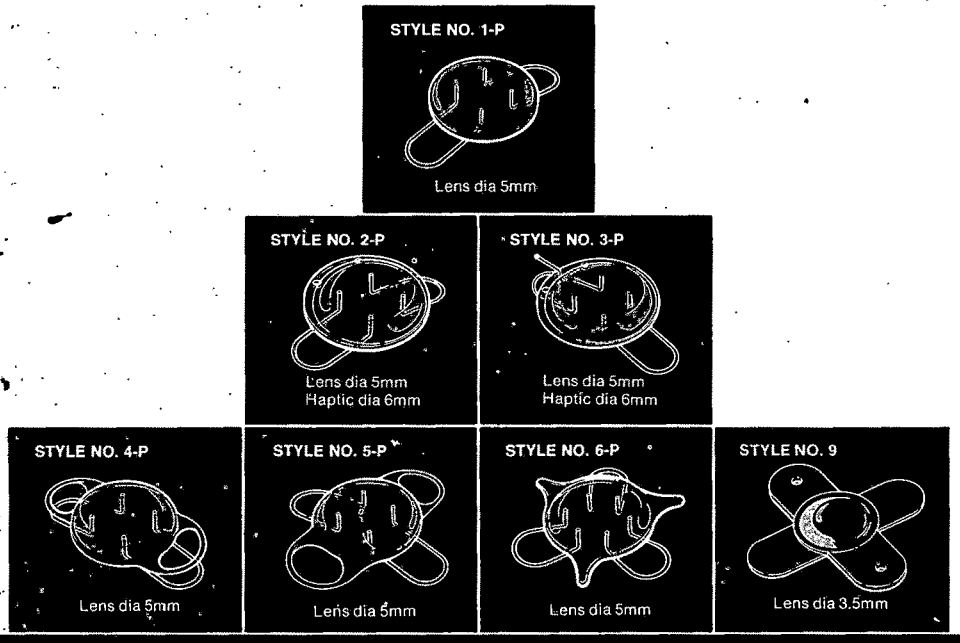
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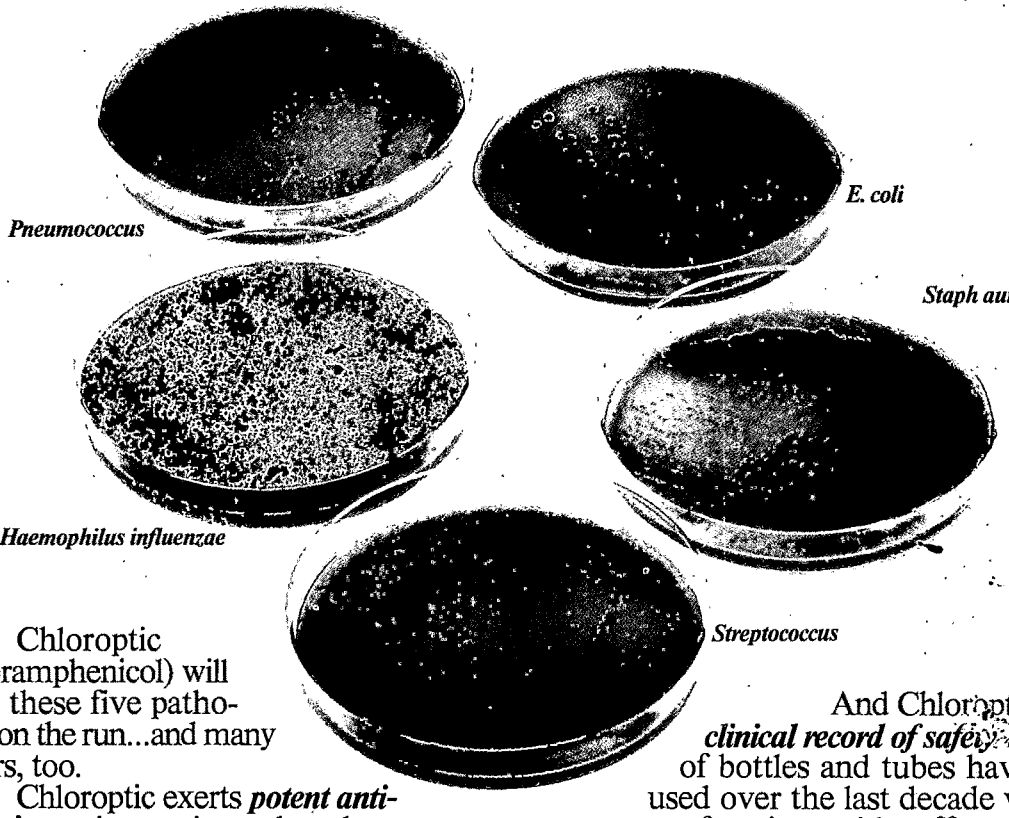
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